

NOVEL ASPECTS OF BENZYLNE CHEMISTRY

by

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Thesis submitted to the University of Nottingham
for the degree of Doctor of Philosophy

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*This Thesis is Dedicated to the Memory of
Natalia Mikhaelovna Yakovleva-Birkett*

DECLARATION

I hereby declare that the substance of this thesis has not been submitted nor is being concurrently presented for any other degree.

I also declare that the work embodied in this thesis is the result of my own investigations and where the work of other researchers has been used, this has been fully acknowledged in the text.

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M.A.BIRKETT

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D.W.KNIGHT

(Director of Studies)

ACKNOWLEDGEMENTS

I wish to take this opportunity to thank the many people who have assisted me in some way during the course of my studies, and the preparation of this thesis.

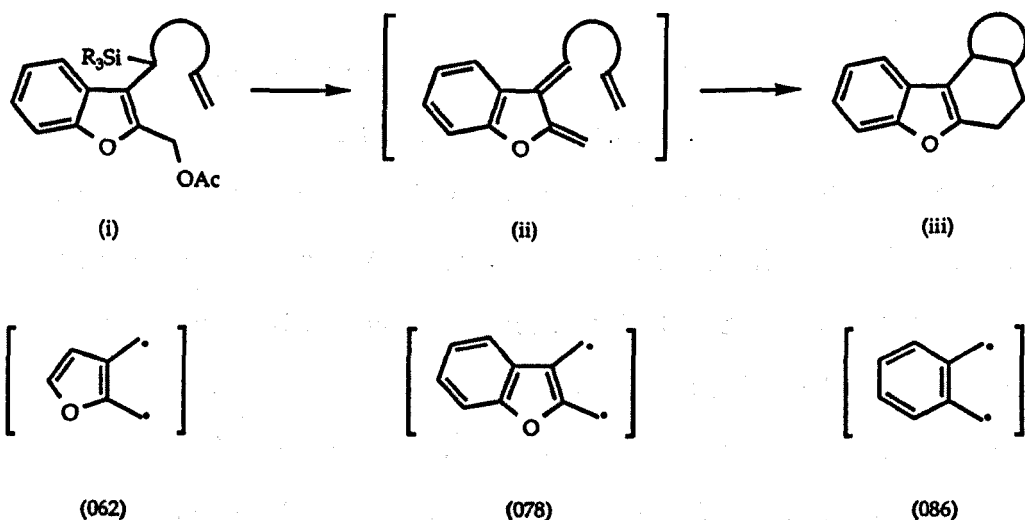
Firstly, I wish to thank my supervisors, David Knight and Michael Mitchell, for their constant support, encouragement and advice, especially throughout the difficult periods of the studies which were encountered and eventually overcome. I would also like to thank the technical staff of the Chemistry Department of the University of Nottingham for their service, and the Science and Engineering Research Council (SERC) and SB Pharmaceuticals for the funding received as part of the CASE award scheme. I am also grateful to the support given by chemists based at SB pharmaceuticals in Tonbridge, in particular Dr Robert Giles, who offered their advice whilst the project was placed at a difficult phase.

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Finally, I am forever indebted to Dulce Maria Fernandez, who has played a major role in keeping me from losing my sanity throughout this testing period in my life, and to whom I owe so much.

ABSTRACT

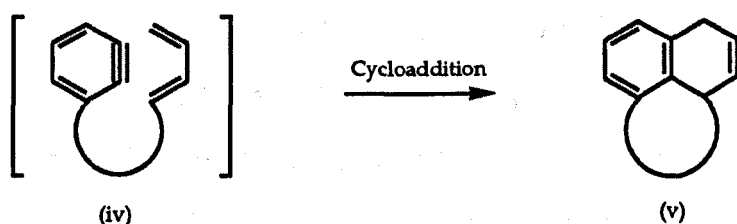
Chapter One describes attempts at utilising *ortho*-quinodimethanes (e.g. *ii*) in the synthesis of polycyclic ring systems (e.g. *iii*), where construction of the the 1,4-elimination precursor (*i*) could not be achieved. Additionally, several attempts were made to utilise the diradical behaviour which *ortho*-quinodimethanes are thought to possess, in similar annulative reactions. Unsuccessful attempts at generating furanyl- (062), benzofuranyl- (078) and benzenoid- (086) derived diradical species, however, brought these particular studies to an end.



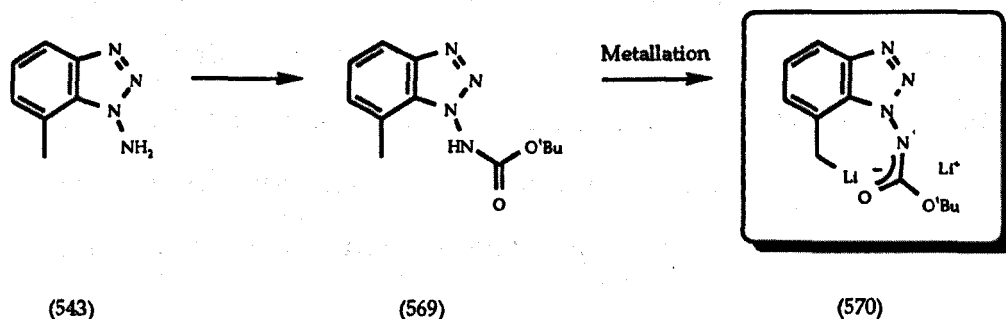
The remainder of this thesis is devoted to studies that were made into developing new uses for benzyne in organic synthesis. Their discovery, general history and subsequent application is divided for convenience into three chapters; Chapter Two covers the discovery of these classic species, and approaches to these species which have been improved from the highly impractical methods which were originally developed. Chapters Three and

Four give an overall review of the past and recently reported applications of benzyne in organic synthesis; Chapter Three covers the use of benzyne in nucleophilic couplings, whilst Chapter Four covers their application in cycloaddition reactions.

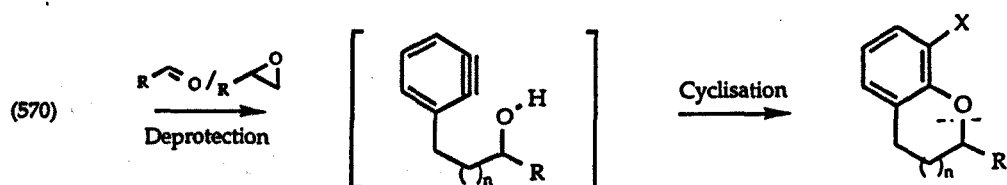
Chapter Five describes preliminary studies that were made into developing new routes to polycyclic ring systems (*e.g. v*) *via* the intramolecular Diels-Alder trapping of benzyne (*e.g. iv*).



After unsuccessful attempts at utilising the anthranilic acid route to benzyne, the remainder of the studies were concentrated on utilising the 1-aminobenzotriazole route to benzyne, a mild, efficient, yet relatively underexploited route. An improved synthesis of 7-methyl-1-aminobenzotriazole (543) is described, as is the functionalisation of the methyl substituent in the BOC-derivative (569) *via* the formation of the dianion (570). However, 1,3-diene incorporation *via* this route was unsuccessful, due to difficulties in preparing suitable 1,3-dienes.



Chapter Six describes attempts at applying the metallation chemistry of BOC-protected 7-methyl-1-aminobenzotriazole (569) to the synthesis of 2-substituted dihydrobenzofurans ($n = 0$) and chromans ($n = 1$) *via* the intramolecular trapping of benzyne by flanking hydroxyl functions, which were incorporated *via* the condensation of the dianion (570) with aldehydes and epoxides respectively. Using *N*-bromosuccinimide as the reagent for benzyne generation, benzo-fused heterocycles were successfully generated in moderate yields, with bromine incorporation also being achieved ($X = \text{Br}$). Using lead(IV) acetate, simple dihydrobenzofurans ($X = \text{H}$) were obtained in better yields. Excellent yields, in some cases virtually quantitative, were obtained using *N*-iodosuccinimide as the reagent, with the iodine substituent ($X = \text{I}$) being incorporated. The additional bonus of having the iodine substituent was highlighted by utilising iodo-dihydrobenzofurans and chromans in subsequent coupling reactions.



Overall, this thesis describes the advances made in increasing the role of benzyne in synthetic organic chemistry, providing novel metallation chemistry on the aminobenzotriazole ring system, and a novel annulative approach to valuable synthetic and potentially active species such as dihydrobenzofurans and chromans. Above all, this work illustrates that under certain suitable conditions, benzyne can serve as extremely efficient reactive intermediates in heterocyclic annulations.

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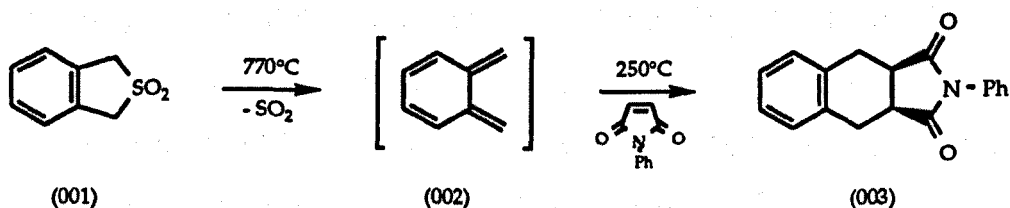
CHAPTER ONE

ortho-Quinodimethanes in Organic Synthesis

- a) *Introduction*
- b) *Heteroquinodimethanes in Organic Synthesis*
- c) *ortho-Methyl Heterocyclic Carboxylic Acids: Precursors of Heteroquinodimethanes*
- d) *Radical Mediated Reactions of ortho-Quinodimethanes*

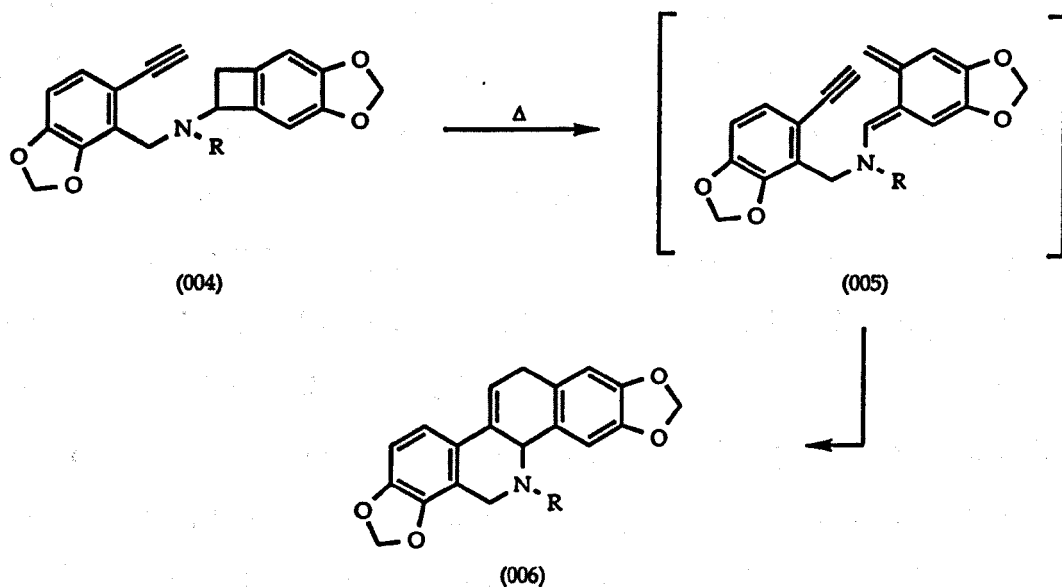
a) Introduction

In the construction of polycyclic ring systems, the requirement of a reactive intermediate in the key annulation step has evolved into one of the most extensively researched areas of modern synthetic Organic Chemistry. One such powerful method is the generation of reactive dienes (known as *ortho*-quinodimethanes or *ortho*-xylylenes) from aromatic systems, and their Diels-Alder trapping, both intermolecularly and especially intramolecularly, leading to the rapid assembly of multi-ring systems.¹ The first published example of an *ortho*-quinodimethane was Finkelstein's quinoid dibromide, generated from a tetrabromoxylene.² Cava and Deana³ reported the synthesis of the 'parent' *ortho*-quinodimethane (002) by extrusion of sulphur dioxide from a number of sulphones (*e.g.* 001), and its trapping with reactive dienes such as *N*-phenylmaleimide (Scheme 1).



Scheme 1

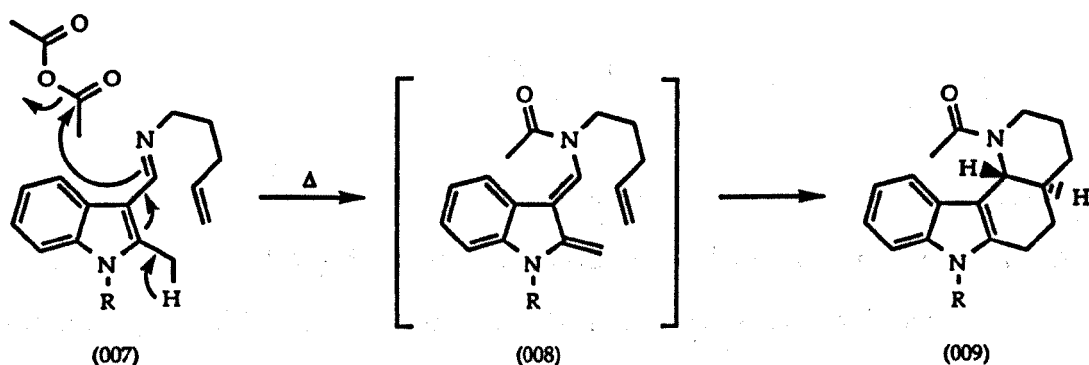
Subsequent synthetic applications of *ortho*-quinodimethanes were slow to appear until Oppolzer⁴⁻⁶ demonstrated the ability to achieve intramolecular cycloadditions using *ortho*-quinodimethane intermediates, applying this chemistry to the synthesis of the naturally occurring alkaloid Chelidonine (Scheme 2).⁶ Oppolzer's successful application has since inspired great interest in these reactive species.⁷



Scheme 2

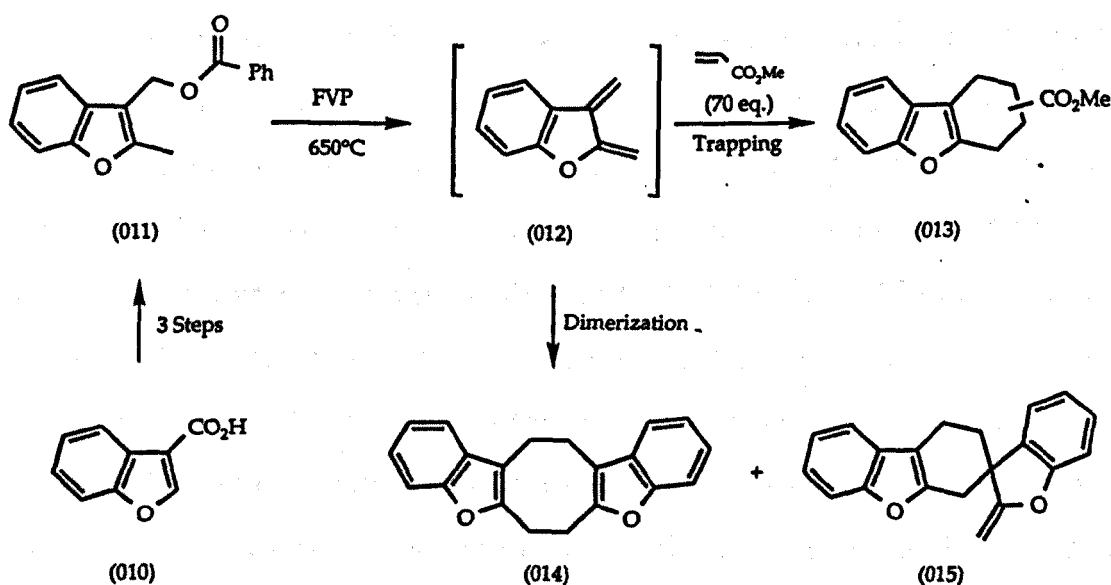
b) Heteroquinodimethanes in Organic Synthesis

Of the heterocyclic quinodimethanes that have been reported in the literature, the indole-2,3-quinodimethane species has been the most extensively studied.⁸ Important work involving the formation of this reactive intermediate was initiated by Gallagher and Magnus, who developed a method based on the thermolysis of indolimines (007), leading to the isolation of annulated indoles (009) (Scheme 3).⁹



Scheme 3

In contrast to the many examples of indole-2,3-quinodimethanes which have been reported since Magnus's pioneering studies, very little work to date has been published on related benzofuran and benzothiophene compounds. An introductory study on the latter by Storr¹⁰ showed that benzothiophene-2,3-quinodimethanes could be generated *via* a flash vacuum pyrolysis [FVP] route, which was originally developed for the generation of the analogous thiophene-2,3-quinodimethane system. Even fewer reports of the occurrence of benzofuran-2,3-quinodimethane (012) have appeared, with the first example being reported by Trahanovsky and Chou,¹¹ in which this reactive species was prepared using FVP in a similar manner to Storr's corresponding thiophene counterpart (*Scheme 4*).



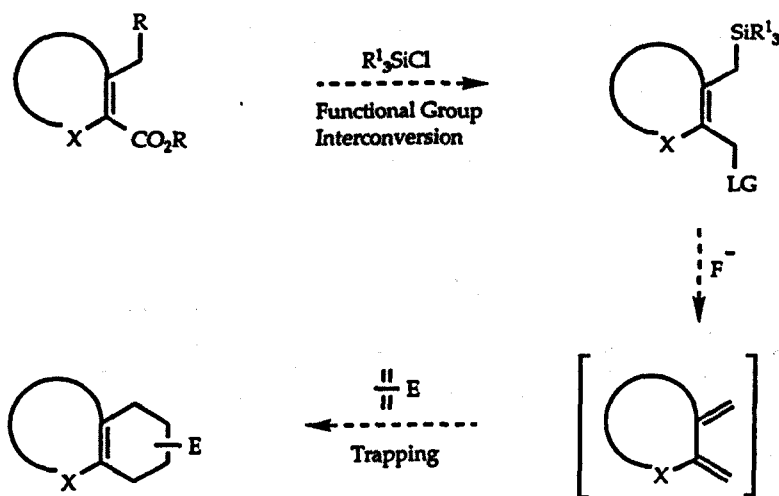
Scheme 4

Preparation of the benzoate precursor (011) was achieved by metallation of 3-benzofurancarboxylic acid (010) and quenching the resulting dianion with methyl iodide to give 2-methyl-3-benzofurancarboxylic acid. The acid was reduced to the alcohol using lithium aluminium hydride, and the alcohol esterified with benzoyl chloride. Upon FVP (650°C @ 10^{-4} Torr), ^1H

NMR spectra showed that low conversion (~ 35%) of the benzoate (011) to the quinodimethane (012) occurred. The stability of the diene in carbon disulphide at low temperatures was also apparent, but at ambient temperatures, the quinodimethane was found to dimerise in two ways, giving the [4 + 4] (014) and [4 + 2] (015) adducts, with the latter predominating in a ratio of 4:1. Additionally, a regioisomeric mixture of Diels-Alder adducts (013) using a vast excess of methyl acrylate was successfully formed, although in a low yield of 30%.

c) *ortho*-Methyl Heterocyclic Carboxylic Acids: Precursors of Heteroquinodimethanes

Of the few routes to heteroquinodimethanes that have been previously reported, the rather non-synthetically useful FVP technique has been mainly used, where quinodimethane generation is achieved with moderate success under very forcing conditions, and the use of vast excesses of dienophile is required in order to generate viable adduct yields. In addition to this, a recurring interest in the Knight group at Nottingham has been the metallation of *ortho*-methyl heterocyclic carboxylic acids and their subsequent functionalisation with a variety of electrophiles.¹²⁻¹⁵ Combining both factors, Knight envisaged a synthetic route to heterocyclic quinodimethanes using a non-FVP route, where functionalisation of *ortho*-methyl substituted heterocyclic carboxylic acids with silylating agents such as chlorotrialkylsilanes, followed by functional group interconversion, would give a quinodimethane precursor possessing a 1,4-relationship between the silyl substituent and the leaving group. Using established fluoride-induced elimination methods,¹⁶ the reactive diene should be generated and subsequently trapped with suitable dienophiles (*Scheme 5*).

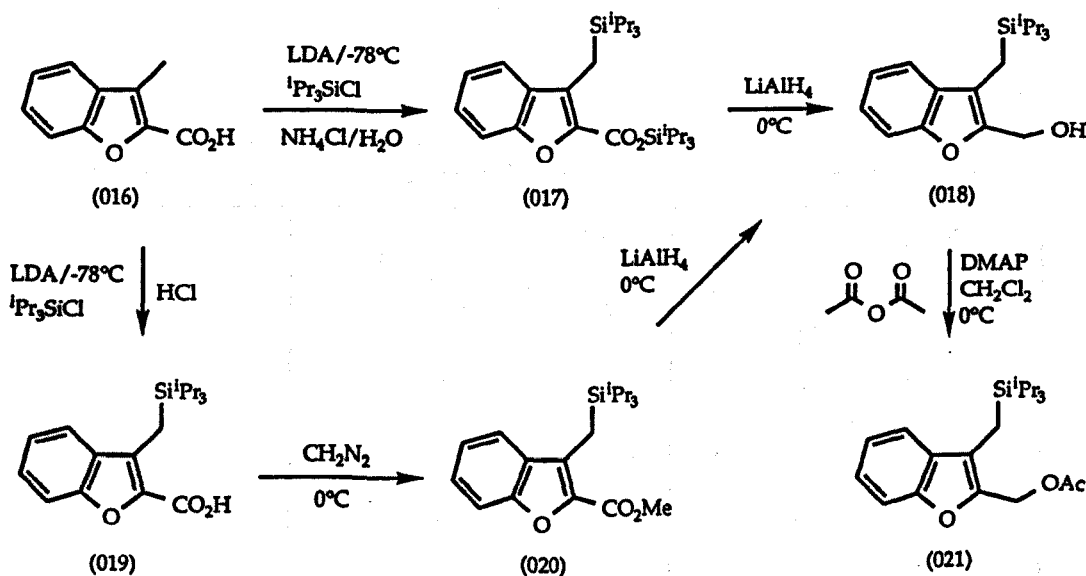


Scheme 5

Intermolecular Reactions of Benzofuran-2,3-quinodimethane (012)

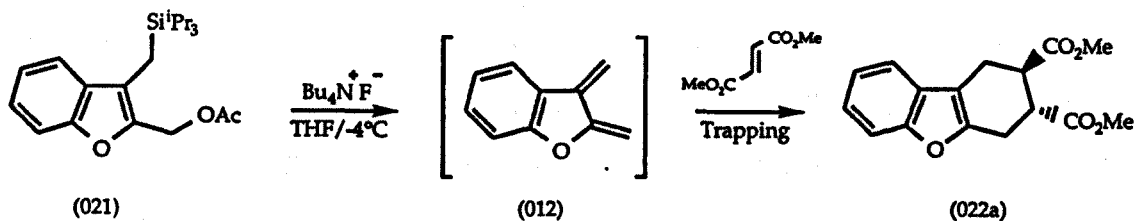
A more specific area of interest in the preparation of heteroquinodimethanes from *ortho*-methyl heterocyclic carboxylic acids has concerned the generation of benzofuran-2,3-quinodimethane (012), of which only one rather non-synthetically useful pyrolytic route had been previously reported (see page 4). Bedford and Knight¹⁷ proposed a more attractive, milder, non-FVP route to this particular reactive diene in which 1,4-precursors could be generated from 3-methylbenzofuran-2-carboxylic acid (016) in the manner outlined above (Scheme 6). With preliminary studies revealing that the trimethylsilyl [TMS] (similar to Magnus's studies on indole quinodimethanes) and *tert*-butyldimethylsilyl [TBDMS] groups were too labile for such a fragmentation process, the acid was silylated with triisopropylsilyl [TIPS] chloride to give the silyl ester (017). Reduction of the silyl ester without prior isolation was accomplished using lithium aluminium hydride in diethyl ether to give the silyl alcohol (018), which was acetylated using acetic anhydride and 4-dimethylaminopyridine [DMAP] to give the silyl acetate (021), a potential quinodimethane precursor.

Additionally, the silyl acid (019^{''}, which was formed by acidic work-up of the silyl ester, was esterified with diazomethane and the silyl ester (020) reduced in a similar manner to give the silyl alcohol.



Scheme 6

Initial attempts at benzofuran-2,3-quinodimethane (012) generation were made using modified Saegusa and Ito conditions,¹⁶ consisting of refluxing the precursor in acetonitrile with tetra-*n*-butylammonium fluoride [TBAF] to produce fragmentation, instead of caesium fluoride as used originally, and featuring dimethyl fumarate as the dienophile. Three major products were isolated; the desired Diels-Alder adduct (022a) in 69% yield, along with the [4 + 4] (014) and [4 + 2] (015) dimers of the *ortho*-quinodimethane obtained in a combined yield of 29%. Switching the solvent to refluxing tetrahydrofuran [THF] increased the Diels-Alder adduct yield by 10% and reduced the yields of the dimerisation products, whilst attempting the reactions in THF at -4°C increased the adduct yield further to 75-80%, with yields of the dimerisation products now kept below 10% (Scheme 7).



Scheme 7

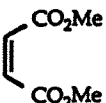
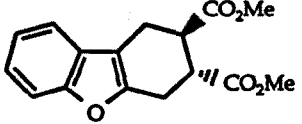
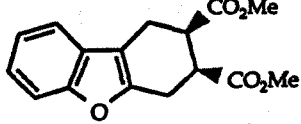
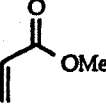
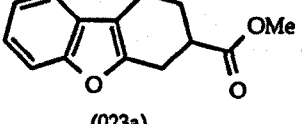
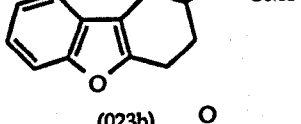
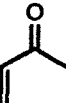
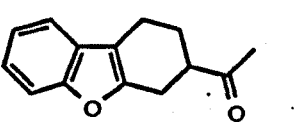
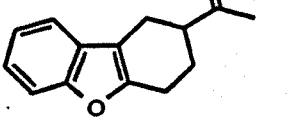

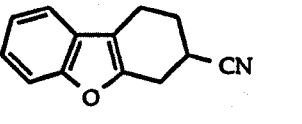
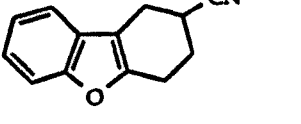
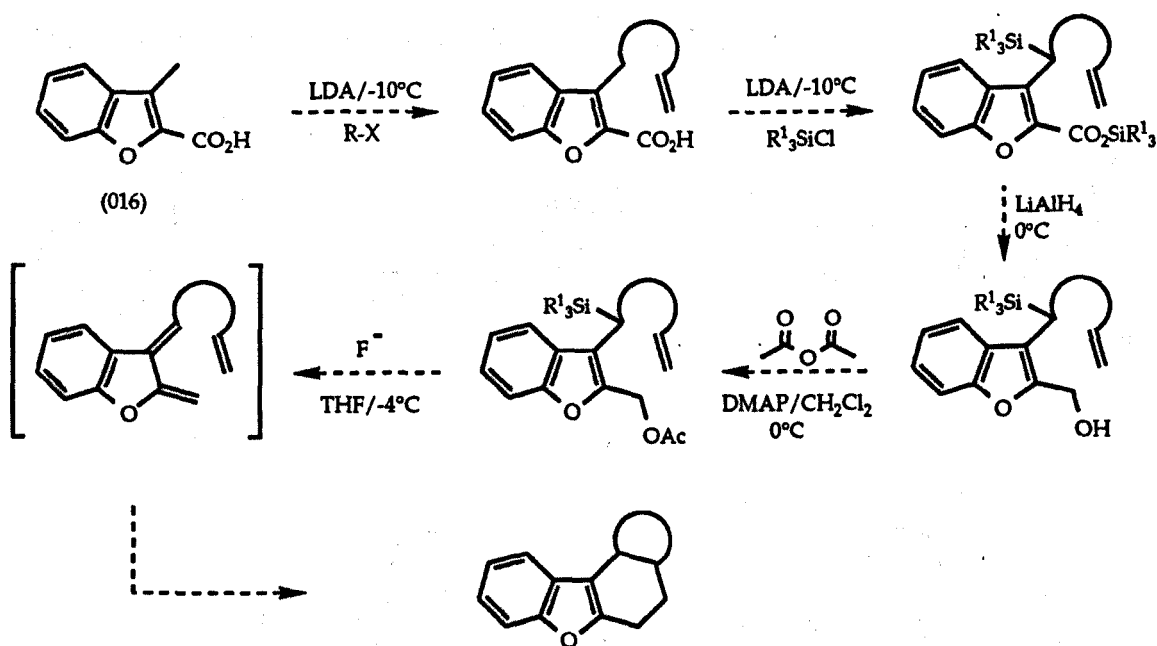
Dienophile	Major Adduct	Minor adduct
	 (022a)	 (022b)
	 (023a)	 (023b)
	 (024a)	 (024b)
	 (025a)	 (025b)

Table 1; Reaction of (012) with Dienophiles

Trapping of benzofuran-2,3-quinodimethane (012) with a series of electron poor dienophiles (specifically dimethyl maleate, methyl vinyl ketone, methyl acrylate and acrylonitrile) were also attempted (Table 1). The reaction with dimethyl maleate gave a combined yield of 69% for the *trans* (022a) and *cis* (022b) adducts with a 2:1 preference for the *trans* isomer, whilst trapping of the quinodimethane with methyl acrylate gave an excellent 85-90% yield of the expected adducts (023a) and (023b) in a 2:1 ratio.

Although methyl vinyl ketone was prone to Michael addition by fluoride, reaction with this dienophile yielded the adducts (024a) and (024b) in a respectable yield of 77% in a regioisomeric ratio of 4:1, whilst trapping with acrylonitrile gave the most selective regiochemical outcome of all the dienophiles used, with the adducts (025a) and (025b) recovered in an excellent yield of 93% and in a 7:1 ratio.

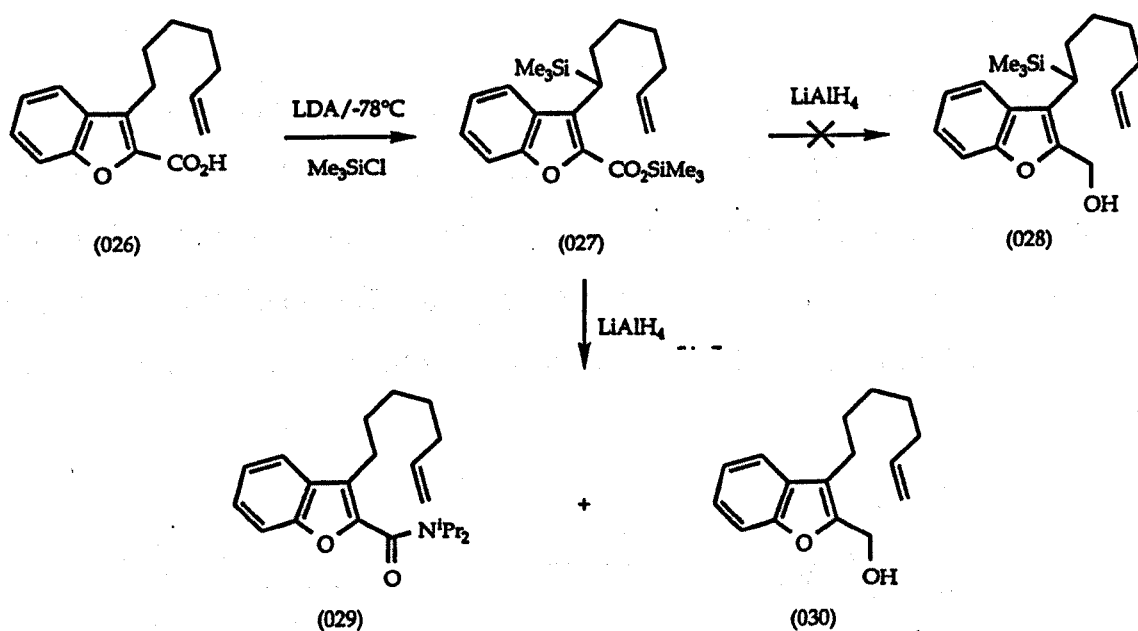
Intramolecular Reactions of Benzofuran-2,3-quinodimethane (012)



Scheme 8

In conjunction with the Knight group's interest in generating benzofuran-2,3-quinodimethane (012), an attractive route to polycyclic compounds *via* the intramolecular trapping of benzofuran-2,3-quinodimethane also received attention (Scheme 8). The advantages which this process would have over the intermolecular version were threefold. Firstly, cycloaddition would appear to be more favourable entropically, as the dienophilic group would be 'held' in place for cyclisation. Secondly,

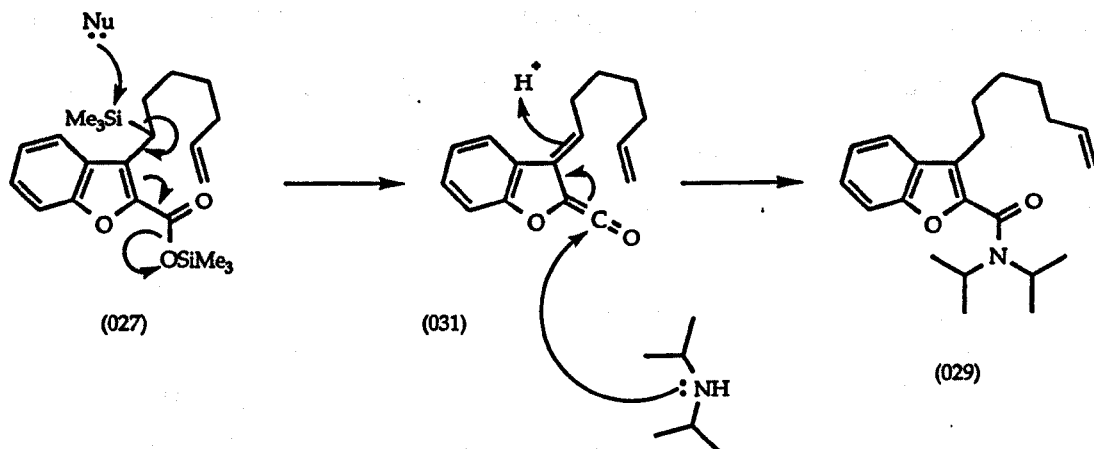
complete regioselectivity would be retained as the dienophile would have to be positioned with a specific orientation relative to the quinodimethane in order to undergo cycloaddition, and finally the requirement of 'activated' dienophiles would also be negated. In initial studies by Cornwall,¹⁸ attempted silylation of the hexenyl-substituted acid (026), generated from 3-methylbenzofuran-2-carboxylic acid (016),¹⁴ with chlorotrimethylsilane followed by reduction of the resulting silyl ester (027) using lithium aluminium hydride, led to the generation of a complex mixture of materials, from which the benzofuran amide (029) and desilylated alcohol (030) were isolated but none of the silyl alcohol (028) (*Scheme 9*).



Scheme 9

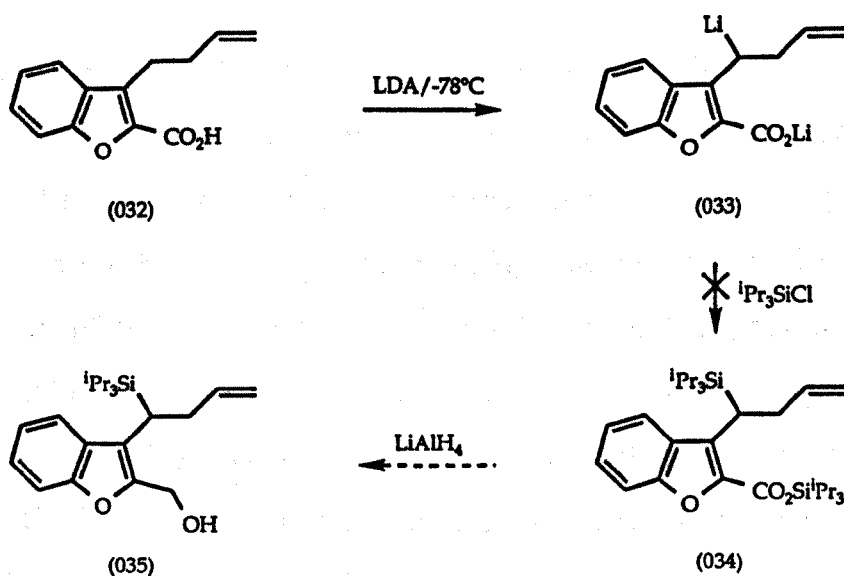
The unexpected isolation of the benzofuran amide (029) was attributed by Cornwall to cleavage of the intermediate silyl ester (027) by a [1,4] elimination process leading to the generation of an α -oxoquinodimethane (031). Regioselective addition of diisopropylamine to this intermediate would then complete formation of the amide (*Scheme 10*). A similar

mechanism was suggested by Rickborn *et al*¹⁹ to explain the conversion of an *ortho*-methyl benzyl ether to an *ortho*-methylbenzylamine derivative.



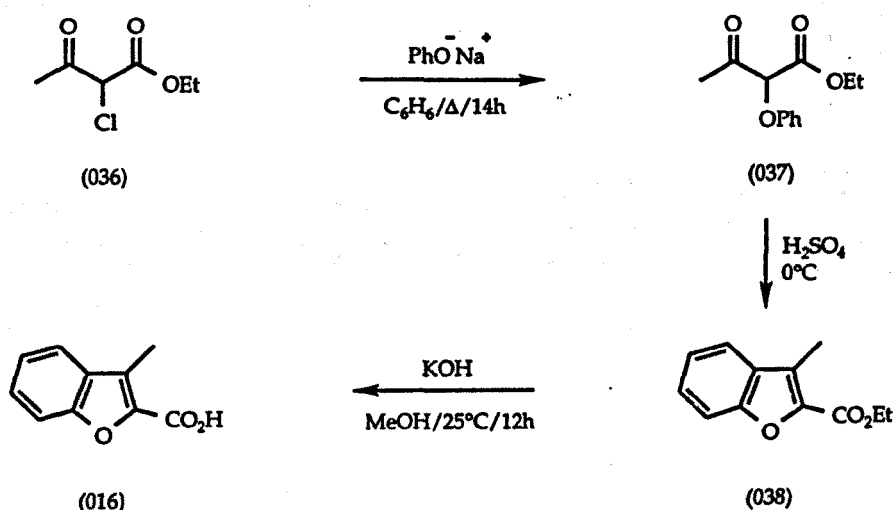
Scheme 10

Bedford⁷ later attempted to apply his preparation of benzofuran-2,3-quinodimethane (012) to this line of work (Scheme 11). Alkylation of the the acid (016) with allyl bromide led to the butenyl acid (032),¹⁴ but attempts to generate the dianion (033), then incorporate the silyl group and reduce the silyl ester (034) *in situ* failed to yield the desired silyl alcohol (035).



Scheme 11

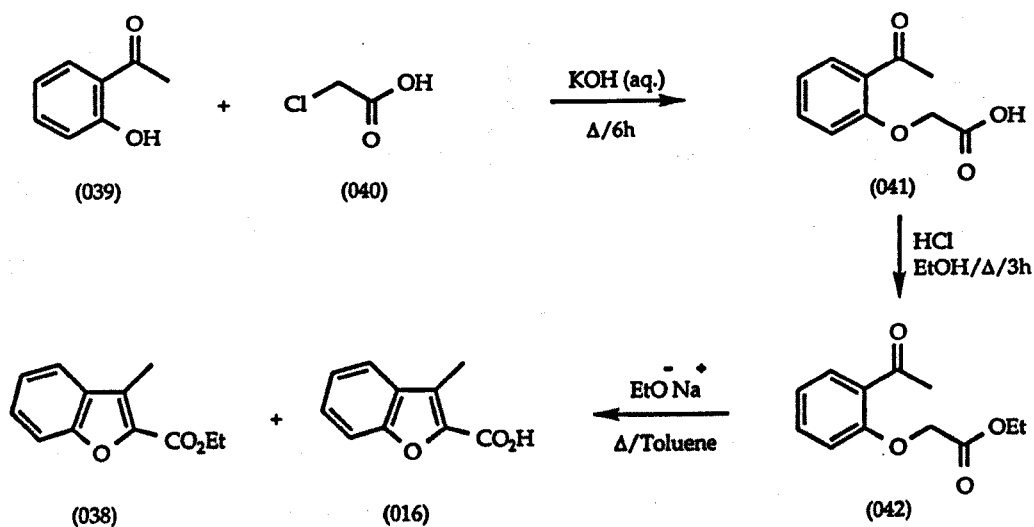
Taking over the project at this stage, our aim was to combine Bedford's efforts at generating a silyl ester of the type (034) using the TIPS group as the silylating agent with the hexenyl-substituted acid (026) with which Cornwall had conducted his studies. Following Boehme's procedure,²⁰ the synthesis of 3-methylbenzofuran-2-carboxylic acid (016) was attempted in three steps starting from commercially available ethyl 2-chloroacetoacetate (036) (Scheme 12).



Scheme 12

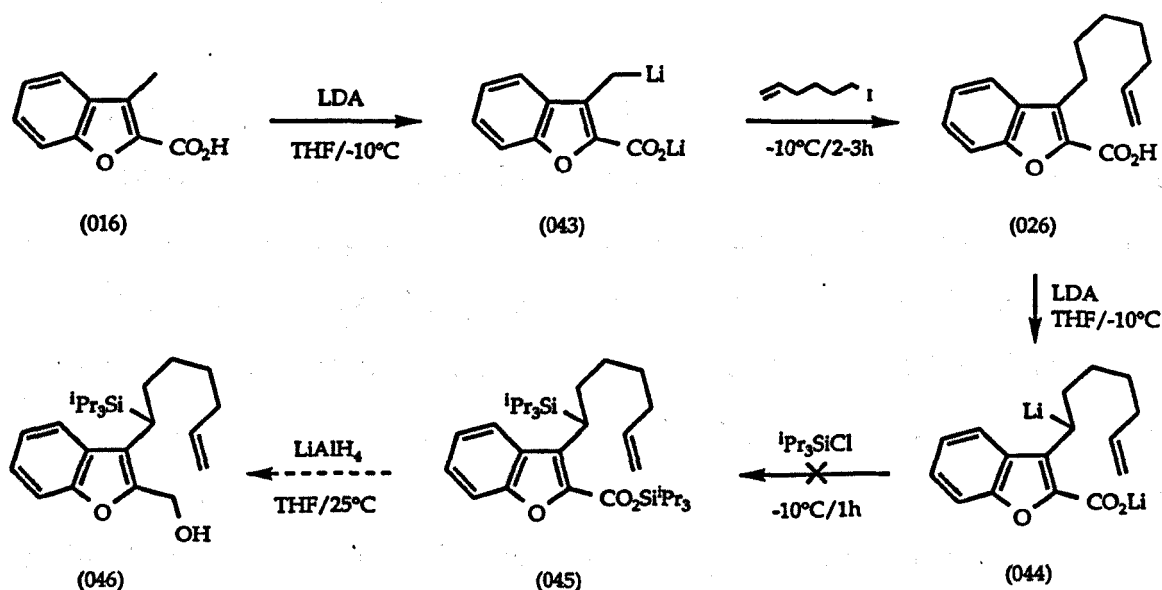
Treatment of ethyl-2-chloroacetoacetate (036) with sodium phenoxide (prepared from phenol and sodium hydroxide) in refluxing benzene gave the required ethyl 2-phenoxy-3-oxobutanoate (037) in moderate yields of 40-50%. Exposure of this keto-ester to ice-cold, concentrated sulphuric acid led to formation of the 3-methylbenzofuran ethyl ester (038) *via* dehydration, although using Bedford's modified work up procedure⁷ failed to prevent large amounts of the product decomposing, resulting in poor yields of 25-35% after distillation. Saponification of the ester was effected by stirring with methanolic potassium hydroxide at ambient temperature, giving the acid

(016) in good yields of 70-80%. The low yields obtained from Boehme's synthetic route prompted a study of alternative syntheses, the most promising of which appeared to be that reported by Wasson *et al*²¹ who showed that the required acid could be prepared from ethyl 2-(2-acetylphenoxy)acetate (042) (Scheme 13).



Scheme 13

In a modification to Wasson's procedure,²² the (acetylphenoxy)acid (041) was generated from commercially available 2-hydroxyacetophenone (039) and chloroacetic acid (040) as a light brown solid in moderate yields of 40-50%. Acid-catalysed esterification of the acid in refluxing ethanol led to the formation of the required ethyl ester (042) as a light brown solid in moderate yields of 45-55%. Treatment of this keto-ester with sodium ethoxide in refluxing toluene gave a separable mixture of the benzofuran acid (016) and ethyl ester (038) in a poor combined yield of 10-20%; subsequent saponification of the ester, as described previously, yielded the acid in 50-60% yield. Although lower yields were obtained than for Boehme's synthesis, sufficient quantities of the acid were obtained to permit further preliminary studies of the key ideas.

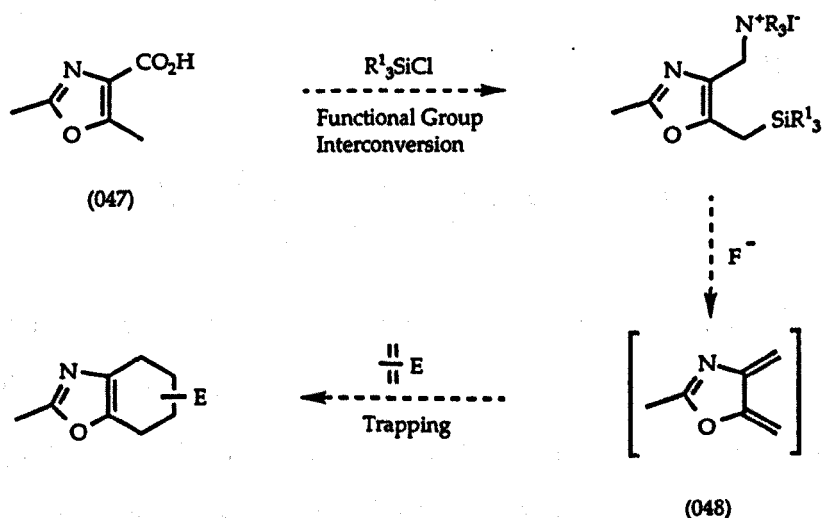


Scheme 14

Repeating the work of Cornwall,¹⁸ the dianion (043) was generated from the acid (016) using lithium diisopropylamide [LDA] in THF at -10°C ,¹⁴ and quenched with one equivalent of 1-iodo-5-hexene, prepared in one step from 5-hexen-1-ol,²³ to give the hexenyl acid (026) as a light yellow solid in good yields of 60-70%. Treatment of the hexenyl acid with LDA at -10°C gave a reddish-orange solution, indicating formation of the dianion (044). Addition of two equivalents of TIPS-chloride at -10°C to this mixture and stirring at this temperature for 1h was followed by the transfer of the presumed silyl ester (045), still in solution, to a vigorously stirred slurry of lithium aluminium hydride in THF at ambient temperature. In a similar manner to Cornwall and Bedford's work, attempted reduction of the ester yielded a complex mixture which resisted chromatographic separation, and which gave no evidence of the formation of the desired silyl alcohol (046). Failure to generate the desired silyl alcohol, coupled with subsequent failed attempts to generate the dianion (044) and quench with the reactive electrophile methyl iodide, spelled the end of our studies in this area.

Reactions of 2,5-Dimethyloxazole-4-carboxylic Acid (047)

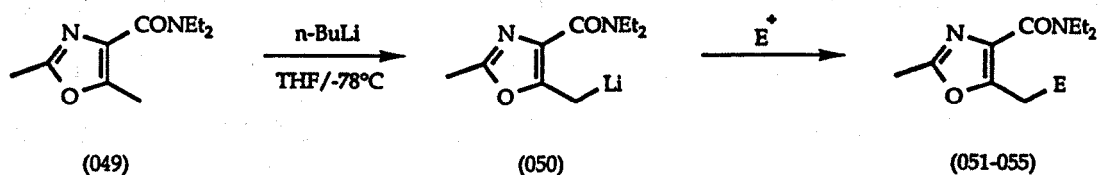
The preparation of oxazole-4,5-quinodimethane (048) has been reported,⁷ amongst others by Storr,²⁴ who generated this reactive intermediate using pyrolytic methods. Continuing their interest in the preparation of heterocyclic quinodimethanes *via* a non-pyrolytic route, the Knight group has attempted the preparation of the quinodimethane (048) from 2,5-dimethyloxazole-4-carboxylic acid (047), using a similar strategy to that previously described for the preparation of benzofuran-2,3-quinodimethane (012). Intermolecular cycloadditions with suitable dienophiles would provide rapid entry into linearly fused [5.6.n] annulated oxazole systems, whilst intramolecular cycloadditions would access angularly fused [5.6.n] annulated oxazole systems (Scheme 15).



Scheme 15

Feasibility studies by Cornwall¹⁸ showed that the N,N-diethylamide group in the oxazole amide (049), derived from the corresponding 2,5-dimethyloxazole-4-carboxylic acid, could be used effectively to promote regioselective lithiation of the 5-position methyl group, as shown by the

isolated yields of the adducts (051-055) obtained by condensation of (050) with a range of electrophiles (*Scheme 16; Table 2*).

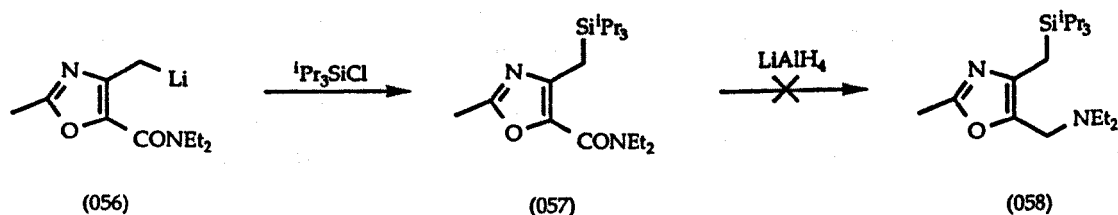


Scheme 16

<u>ELECTROPHILE</u>	<u>PRODUCT</u>	<u>YIELD (%)</u>
CH ₃ I	(051)	98
C ₂ H ₅ I	(052)	97
CH ₂ :CHCH ₂ Br	(053)	98
C ₆ H ₅ CHO	(054)	98
CH ₃ (CH ₂) ₂ CHO	(055)	15

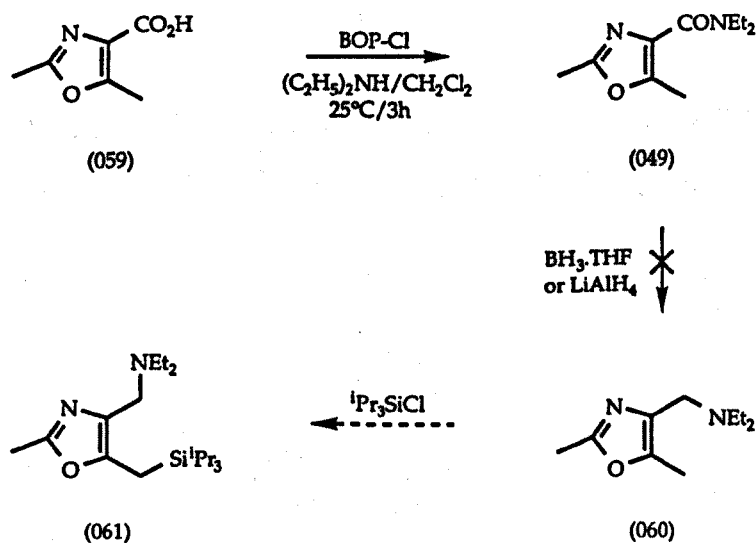
Table 2; Functionalisation of Oxazole (049)

Bedford⁷ went on to demonstrate that the closely related anion (056) could be silylated with TIPS-chloride, but attempted reduction of the silyl amide (057) using lithium aluminium hydride failed to give any of the desired silylated tertiary amine (058) (*Scheme 17*).



Scheme 17

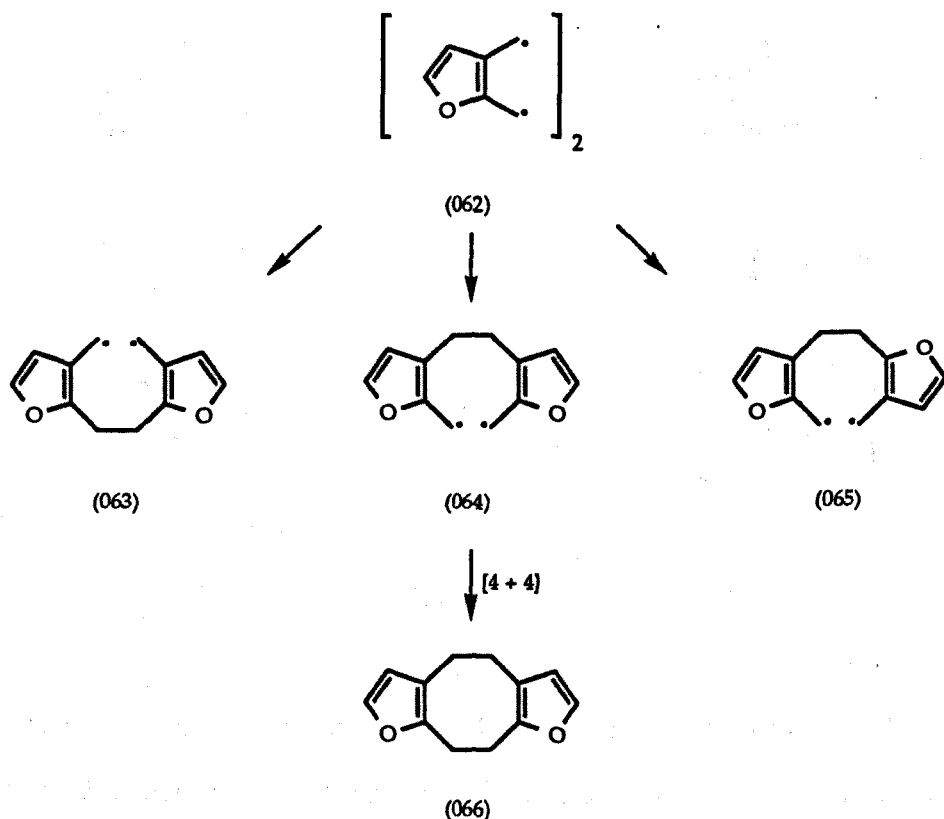
Working on the oxazole amide (049) previously studied by Cornwall, we anticipated that attempted reduction of the silylated amide would also fail to proceed. The approach that we decided to adopt was to initially reduce this amide prior to silylation, potentially eliminating the afore-mentioned problem of reducing a silylated amide (Scheme 18). Thus, preparation of the oxazole amide (049) from 2,5-dimethyloxazole-4-carboxylic acid (059) was attempted following Cornwall's procedure.¹⁸ Treatment of the acid with thionyl chloride in benzene followed by diethylamine led to the required tertiary amide in poor yields of 20-30%. Higher yields of this amide, in the region of 65-75%, were obtained using the efficient one step coupling agent *N,N*-bis-(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride [BOP-chloride]²⁵ in conjunction with diethylamine in dichloromethane at ambient temperature. Attempted reduction of the amide using five equivalents of borane in refluxing THF²⁶ however, failed to yield the amine (060). In a similar manner, attempts to reduce the amide using lithium aluminium hydride in refluxing THF also failed to give this amine, and failure to accomplish this step spelled the end for this particular route.



Scheme 18

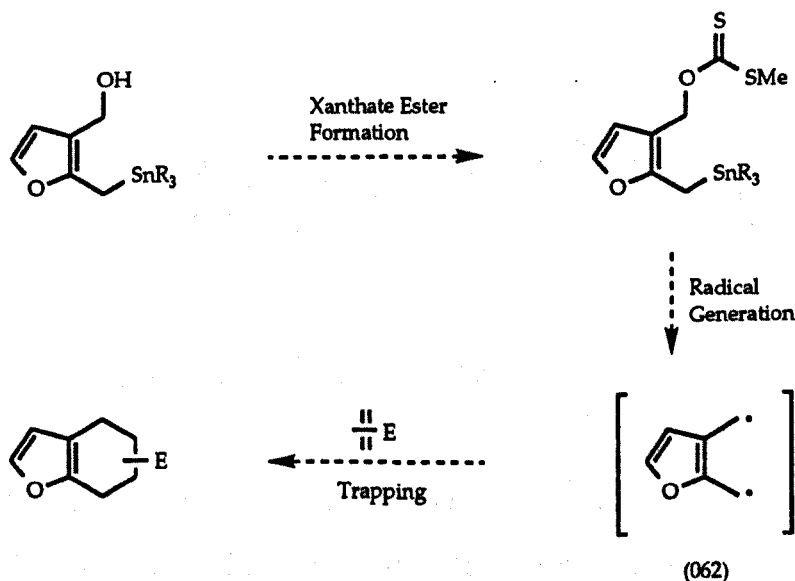
d) Radical Mediated Reactions of *ortho*-Quinodimethanes

It has been suggested, amongst others by Trahanovsky,^{11, 27} that furan-2,3-quinodimethane could possess considerable diradical character, such as that in structure (062). The same author has put forward a convincing argument that a diradical mechanism occurs in the dimerisation of this quinodimethane, suggesting that initial dimerisation could give three possible diradical intermediates [(063), (064) and (065)]; the diradical (064) would be more resonance stabilised than the other diradicals as a result of having more canonical forms available, thus leading to the formation of a single [4 + 4] adduct (066) only. This was later confirmed by the regioselective isolation of this adduct (Scheme 19). A recent kinetic study by the same author²⁸ has indicated that dimerisation occurs *via* a two step process.



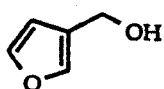
Scheme 19

Assuming that furan-2,3-quinodimethane does possess such radical behaviour, we decided to adopt a strategy that would allow us access to this form of the reactive species, and which could be used to construct new heterocyclic systems *via* an intermolecular radical cycloaddition with suitable trapping agents. Based on Sano and Mitiga's²⁹ procedure of quinodimethane generation *via* the 1,4-elimination of 2-alkylstannyl benzyl alcohols, a suitable route concerned the preparation of the corresponding 2-alkylstannyl furyl alcohols and derivatisation of the alcohol to a xanthate ester, which would be followed by radical generation upon exposure of the ester to a radical initiator.³⁰ Concurrent cleavage of the 2-alkylstannyl group under these conditions would then generate the diradical species (062) (Scheme 20).

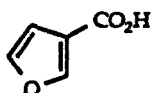


Scheme 20

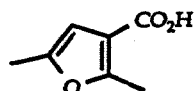
Three furanyl derived compounds were thought to be suitable for this approach; 3-furanmethanol (067), 3-furoic acid (068) and 2,5-dimethyl-3-furoic acid (069), all of which are commercially available (Scheme 21).



(067)



(068)

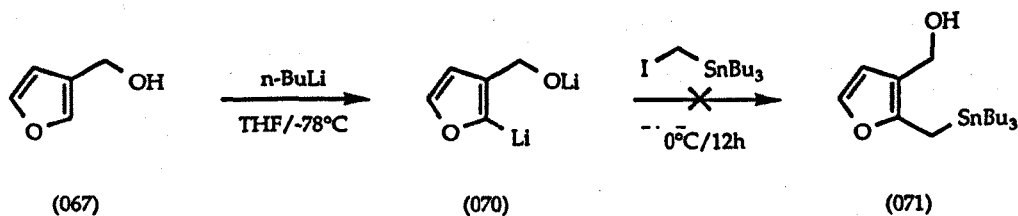


(069)

Scheme 21

Reactions of 3-Furanmethanol (067)

A previous report by Goldsmith *et al*³¹ which claimed that treatment of 3-furanmethanol with two equivalents of *n*-butyllithium in THF at -78°C would lead to the formation of the dianion (070), led us to believe that stannylation of the dianionic species with iodomethyltri-*n*-butylstannane would yield the desired alcohol (071) prior to derivatisation to the xanthate ester (Scheme 22).



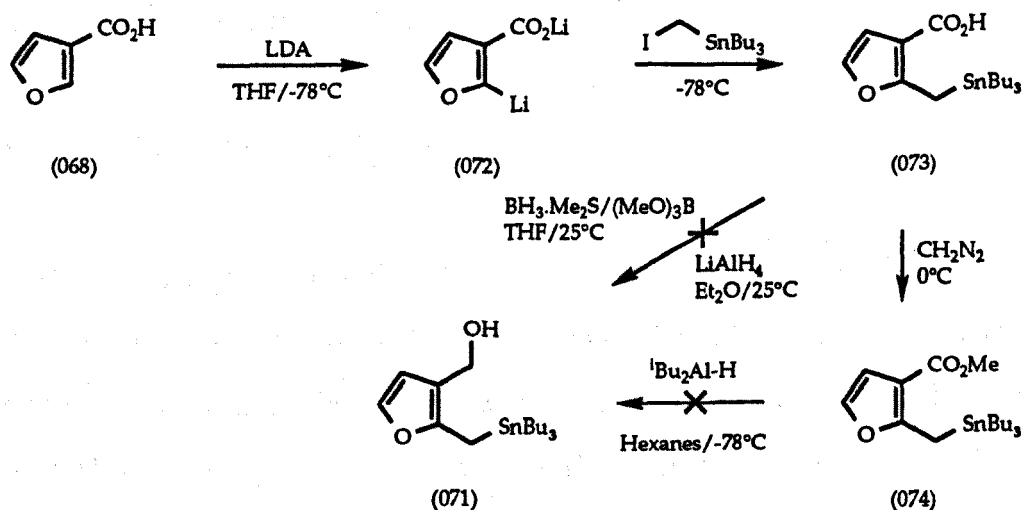
Scheme 22

Preparation of iodomethyl-*n*-butylstannane as a light yellow distillable oil (b.p. 110°C @ 0.5 mmHg) from chlorotri-*n*-butylstannane³² was achieved in high yields of 70-75%. After apparently generating the dianion from 3-furanmethanol using *n*-butyllithium as previously described, addition of one equivalent of iodomethyltri-*n*-butylstannane at -78°C failed to yield any of the desired product (071), with spectroscopic analysis of the crude material suggesting that starting material had been recovered. Failure to quench the dianionic species (070) with one equivalent of diphenyl disulphide as

previously described by Goldsmith *et al* spelled the end for this particular scheme.

Reactions of 3-Furoic Acid (068)

Previous studies in the Knight group¹² had shown that the dianionic species (072) could be generated from 3-furoic acid (068) upon treatment with two equivalents of LDA in THF at -78°C , and could be selectively alkylated at the 2-position upon addition of suitable electrophiles. In a similar manner to the scheme starting from 3-furanmethanol, we envisaged that the dianion could be homologated with iodomethyltri-*n*-butylstannane, and the carboxylic acid group in compound (073) could then be reduced to give the stannyl alcohol (071) (Scheme 23).



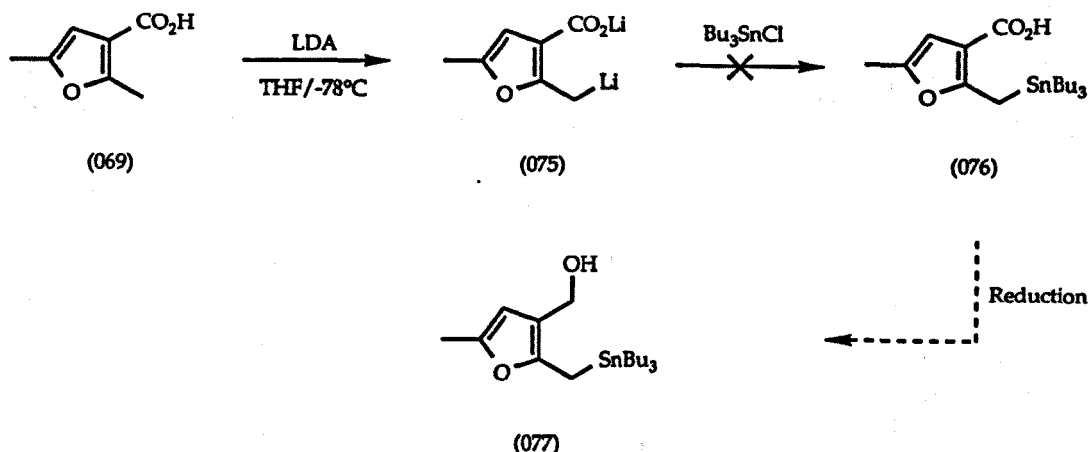
Scheme 23

Following Knight's procedure,¹² addition of 3-furoic acid (068) to a solution of two equivalents of LDA in THF at -78°C generated the dianion (072), which was treated with one equivalent of iodomethyltri-*n*-

butylstannane at -78°C to give the stannylated furoic acid (073) as a light yellow oil in excellent yields of 90-95%. Attempts to reduce the acid to the stannyl alcohol (071) using borane-methyl sulphide³³ as reducing agent in the presence of trimethylborate at ambient temperature were unsuccessful, with the starting material being retrieved. Using two equivalents of lithium aluminium hydride in diethyl ether at ambient temperature did, however, give a crude material which appeared to contain the stannyl alcohol upon spectroscopic analysis, but this material could not be purified prior to derivatisation. Instead of attempting to reduce the acid to the alcohol, esterification of the acid using diazomethane gave the methyl ester (074) as a light yellow oil in virtually quantitative yield, and attempted reduction of the ester using diisobutylaluminium hydride [DIBAL-H] in *n*-hexane at -78°C yielded a crude material which appeared from spectroscopic analysis to be mainly the alcohol (071). Once again, our efforts were frustrated by the failure to retrieve the alcohol upon attempted purification, and so the project was stopped at this stage.

Reactions of 2,5-Dimethyl-3-furoic Acid (069)

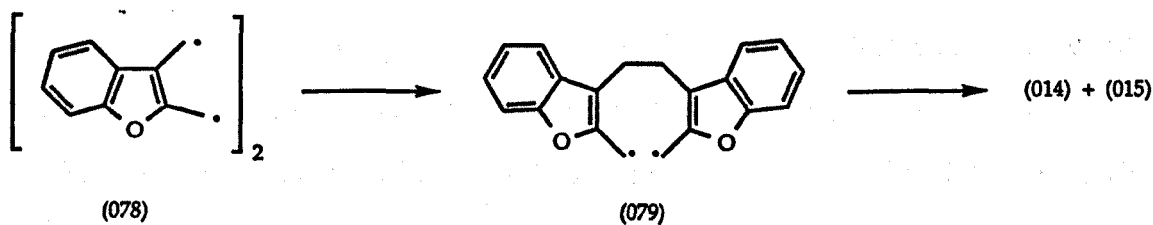
Previous reports on the deprotonation of 2,4-dimethyl-3-furoic acid (069) upon exposure to two equivalents of LDA in THF at -78°C and quenching with a series of electrophiles,³⁴ inspired a brief look at the potential for using a similar metallation strategy on the 2,5-dimethyl analogue (069), with the resulting dianion (075) being stannylated at the 2-methyl position using chlorotri-*n*-butylstannane, to give the stannylated acid (076) (Scheme 24). However, failure to achieve complete dianion formation from acid (069) was made apparent by the isolation of mixtures of starting material and product when methyl iodide was used as the electrophile; failure to accomplish this step spelled the end for this route.



Scheme 24

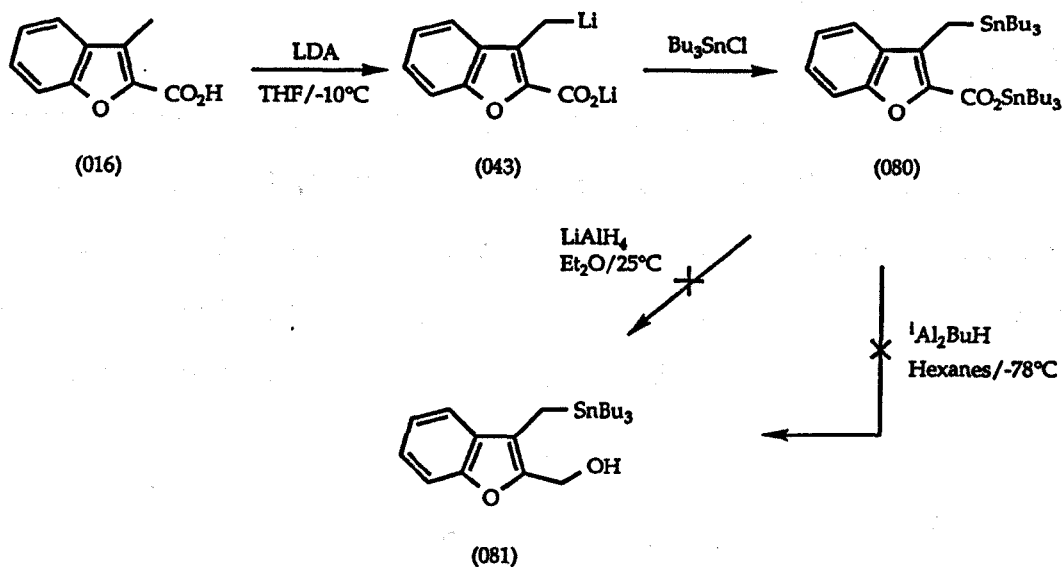
Reactions of 3-Methylbenzofuran-2-carboxylic Acid (016)

During their studies on benzofuran-2,3-quinodimethane (012) generation, Trahanovsky and Chou¹¹ suggested that the isolation of the [4 + 4] (014) and [4 + 2] (015) dimers was indicative of diradical character in this reactive intermediate (078) (Scheme 25).



Scheme 25

Assuming that benzofuran-2,3-quinodimethane (012) possessed a certain degree of diradical nature, we attempted to apply our strategy for generating the furan-2,3-quinodimethane diradical (062) to the generation of the diradical form of benzofuran-2,3-quinodimethane (078), again attempting construction of a stannyl alcohol (081) prior to derivatisation and trapping of the reactive species with trapping agents (Scheme 26).



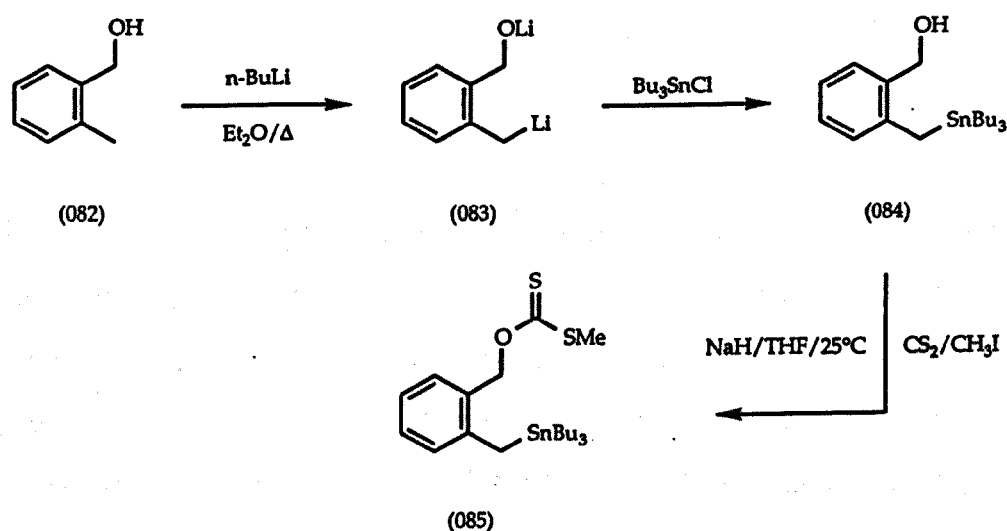
Scheme 26

Treatment of the dianion (043), generated from the acid (016) using LDA as previously described, with two equivalents of chlorotri-*n*-butylstannane yielded the *bis*-stannyl ester (080) as a yellow oil in good yields of 70-80%. Reduction of the ester using lithium aluminium hydride in diethyl ether gave a crude material which appeared upon spectroscopic analysis to be the stannyl alcohol (081). Once again, however, the crude material could not be purified. Reduction of the ester using DIBAL-H in THF at -78°C gave a mixture of materials which again appeared to be mainly the stannyl alcohol by spectroscopic analysis. Yet again, the product could not be retrieved upon attempted purification; this frustrating inability to purify the stannyl alcohol meant that this line of work could not be continued.

Reactions of 2-Methylbenzylalcohol (082)

The difficulties experienced in attempting to generate diradical intermediates of either furans or benzofurans forced us to look at the

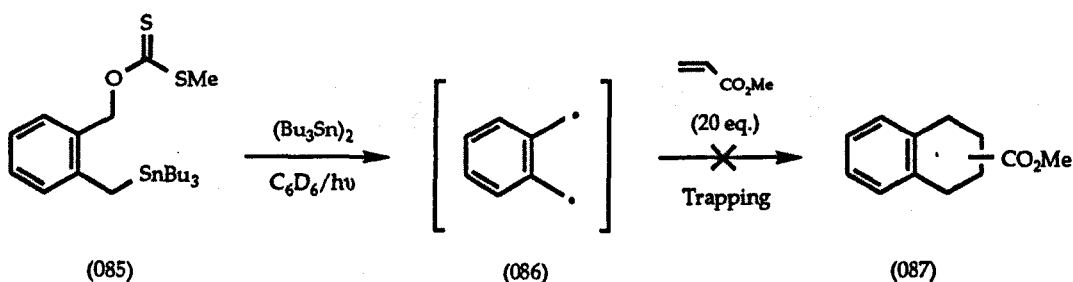
possibility of generating the diradical form of the 'parent' *ortho*-quinodimethane. In an analogous manner to Sano and Mitiga's approach,²⁹ stannylation of the dianion (083) generated from commercially available 2-methylbenzylalcohol (082) would give the corresponding stannyl alcohol (084), but instead of using the alcohol to generate the quinodimethane as Sano and Mitiga had achieved, derivatisation of the alcohol would give the radical precursor (085) for our studies (Scheme 27).



Scheme 27

Treatment of the alcohol (082) with two equivalents of *n*-butyllithium in refluxing diethyl ether³⁵ gave the dianion (083), which was cooled to 0°C before the addition of one equivalent of chlorotri-*n*-butylstannane to give the stannyl alcohol (084) as an amber coloured oil in very good yields of 85-90% after distillation (b.p. 100°C @ 5mmHg). Xanthate ester formation³⁰ was then effected by treatment of the stannyl alcohol initially with sodium hydride and catalytic imidazole in THF at ambient temperature, followed by the addition of three equivalents of carbon disulphide and finally methyl iodide, with the product (085) obtained as a light yellow oil, in a good yield of 70%.

Preliminary studies on diradical (086) generation were then attempted on NMR tube scales, with intermittent ^1H NMR analysis providing evidence of any reactions proceeding (Scheme 28).



Scheme 28

Using non-reducing conditions, a mixture of the xanthate ester (085) and an excess of methyl acrylate in the presence of catalytic hexabutyldistannane $[(\text{Bu}_3\text{Sn})_2]$ using deuteriated benzene as solvent was subjected to irradiation by Ultra-Violet [UV] light and analysed spectroscopically every 30 minutes. ^1H NMR and thin layer chromatography (tlc) analysis indicated the gradual disappearance of the starting material and the formation of a number of components. However, no sign of any of the desired product (087) appeared to be present. Repeated reactions under identical conditions again failed to indicate any formation of the desired adducts, as did attempted radical generation using tri-*n*-butyltin hydride and AIBN in the presence of *N*-methylmaleimide; failure to perform this step resulted in drawing our studies on *ortho*-quinodimethanes to an end.

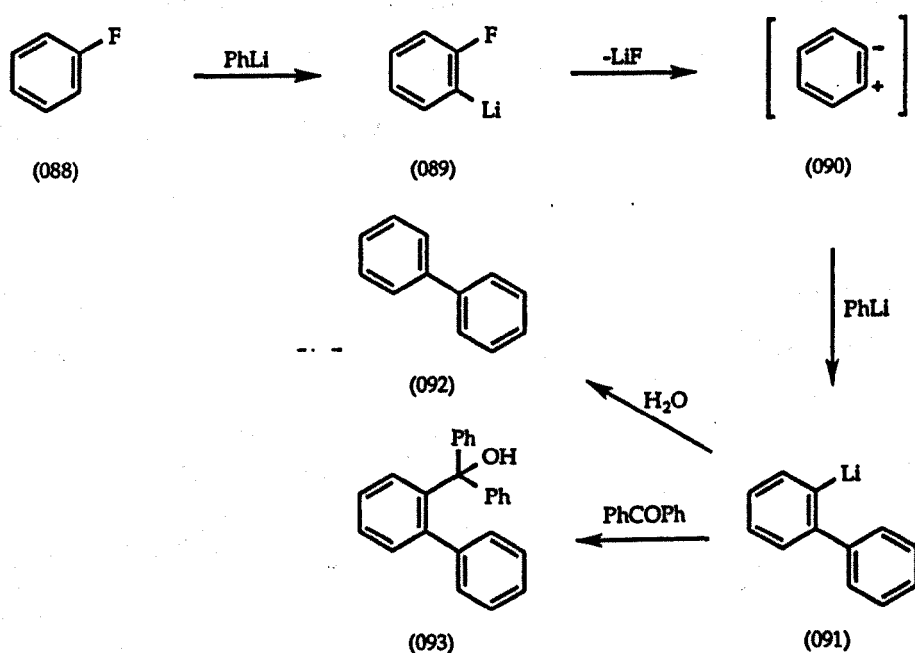
CHAPTER TWO

An Introduction to Benzyne

- a) *General History*
- b) *Structure and Reactivity of Benzyne*
- c) *Approaches to Benzyne*

a) General History

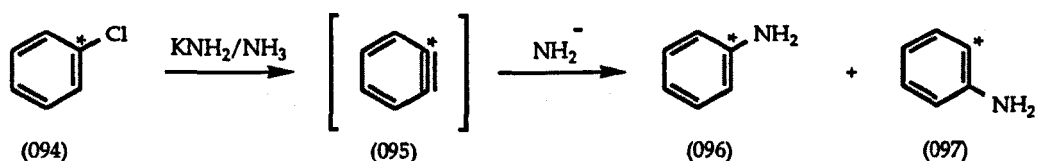
Benzynes are considered to be one of the classic reactive intermediates in organic chemistry.^{36, 37} These highly unstable, neutral species can be formally generated from aromatic systems by the removal of two hydrogens. The existence of the parent species, *ortho*-benzyne, C_6H_4 , was suggested as early as 1902³⁸ in order to explain the occurrence of *cine* substitution in certain reactions, but no decisive evidence was forwarded until Wittig³⁹ incorrectly postulated a polar intermediate (090) for the action of phenyllithium on fluorobenzene (088) (Scheme 29).



Scheme 29

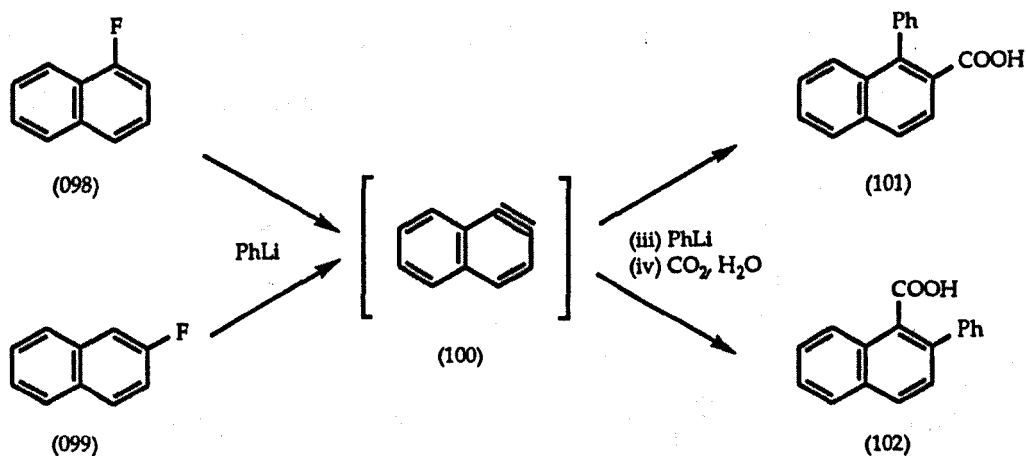
Nearly a decade later, the symmetrical identity of *ortho*-benzyne was revealed by Roberts,⁴⁰ who showed that nearly equal amounts of 1- ^{14}C -aniline (096) and 2- ^{14}C -aniline (097) were isolated upon treatment of ^{14}C -labelled chlorobenzene (094) with potassium amide in liquid ammonia,

suggesting that a symmetrical intermediate (095) was generated during the course of the reaction (Scheme 30).



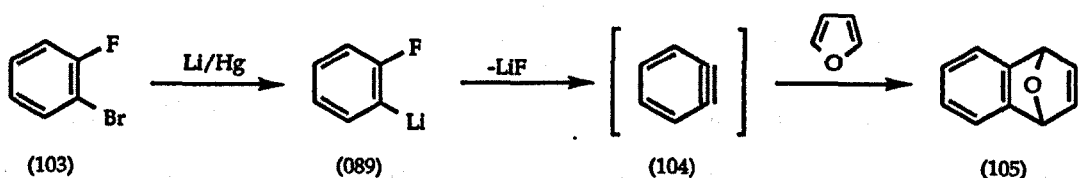
Scheme 30

Further evidence for the symmetrical intermediate came from Huisgen,⁴¹ who showed that treatment of 1- and 2-fluoronaphthalenes (098) and (099) with phenyllithium, and subsequent trapping of the 1,2-naphthalene (100) with phenyllithium and carbon dioxide yielded the predicted 2:1 ratio of 1-phenyl-2-naphthoic acid (101) and 2-phenyl-1-naphthoic acid (102) respectively (Scheme 31).



Scheme 31

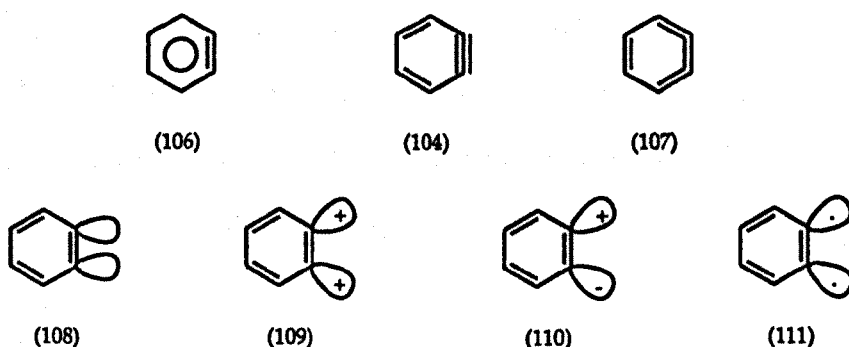
Wittig⁴² later reaffirmed the symmetrical nature of the reactive intermediate when he isolated 1,4-epoxy-1,4-dihydronaphthalene (105) from the reaction of *ortho*-fluorobromobenzene (103) with lithium amalgam in the presence of furan (Scheme 32).



Scheme 32

b) Structure and Reactivity of Benzyne

The structure of the parent species, *ortho*-benzyne (104), has been subjected to much experimental and theoretical study. Force field calculations based on the observed IR spectrum of *ortho*-benzyne,⁴³ (which is generated upon low temperature solid matrix photolysis of precursors such as benzocyclobutanedione)⁴⁴⁻⁴⁷ along with the observed microwave⁴⁸ and photoelectron⁴⁹ spectra and *ab initio* studies, have all indicated an extended triple bond which is longer than a normal triple bond, from which the 'yne' nomenclature arises, while the other C-C bonds are similar in length to those in benzene.⁵⁰



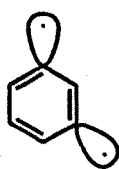
Scheme 33

Although recent *ab initio* studies suggest more cumulene like features (107) in *ortho*-benzyne,⁵¹ the weak, easily polarised third bond in (104) and

(106) can be considered to be formed by lateral overlap of in-plane orbitals in (108). The symmetric combination (109) of the two orbitals is lower in energy than the antisymmetric combination (110), and so the ground state of benzyne should be considered to be a singlet, not a triplet state. Alternatively, the reactive species could be drawn in a diradical manner (111), although its chemistry on the whole indicates triple bond behaviour.

The reactivity of *ortho*-benzyne can be explained by considering its orbital energy levels. Although the Highest Occupied Molecular Orbital [HOMO] energy of *ortho*-benzyne has been calculated to be comparable to that of linear acetylenes such as but-2-yne, the Lowest Unoccupied Molecular Orbital [LUMO] energy is calculated at a value much lower than that of the acetylene, which has been attributed to the bending of the triple bond within the ring structure.⁵² The subsequent lowering of the LUMO decreases the energy gap between *ortho*-benzyne and the HOMO of an attacking nucleophile, making these species highly electrophilic. Consequently, attack by nucleophiles occurs in a facile manner, even with relatively inert species (see Chapter Three). Additionally, the strained triple bond behaves as a highly reactive alkyne and will participate in cycloadditions of various types, even with unreactive partners (see Chapter Four).

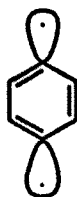
In addition to *ortho*-benzyne, the removal of two hydrogens from the *meta* and *para* positions of benzene leads to the formation of *meta* and *para* isomers of benzyne respectively.



(112)



(113)



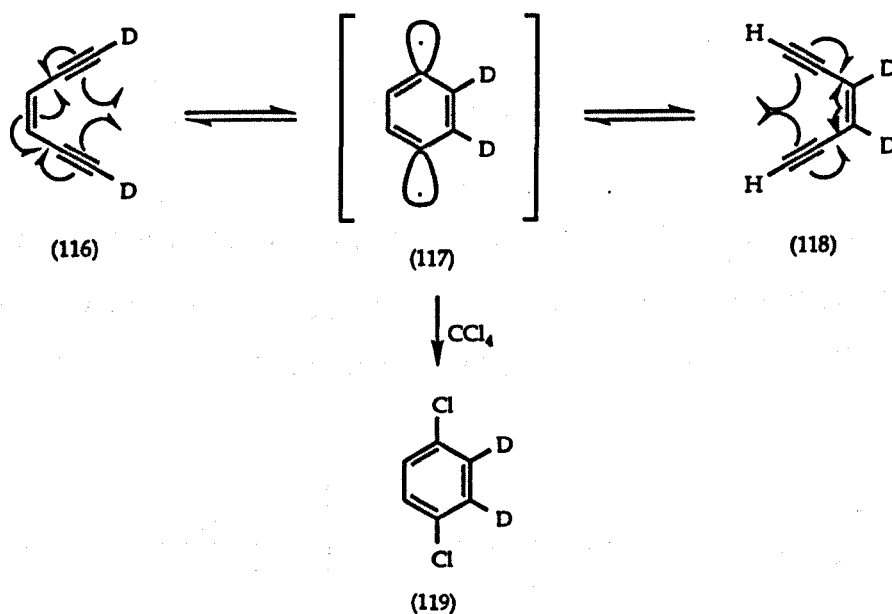
(114)



(115)

Scheme 34

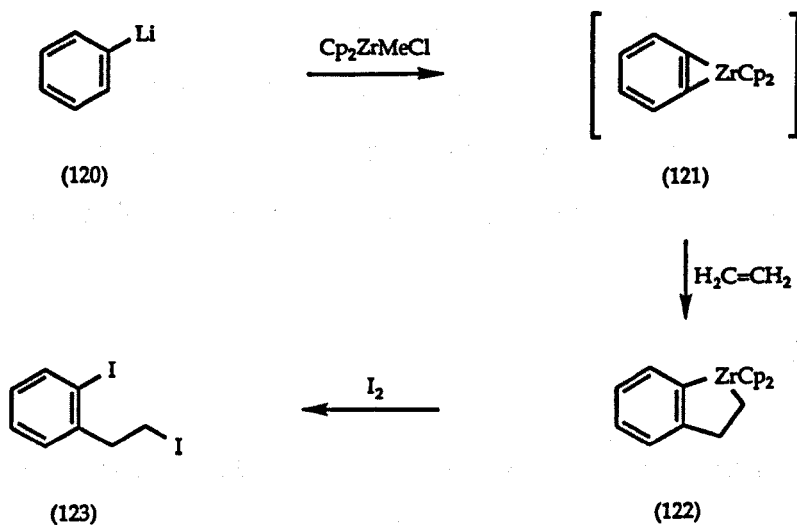
Although the structures can be represented as either diradicals or bicyclic compounds, experimental evidence suggests that for *meta*-benzyne, the bicyclic structure (113) appears to be more stable despite appearing to be more strained than the 1,3-diradical (112) (Scheme 34). For *para*-benzyne, the diradical form (114) appears to be more stable than the highly strained bicyclic form (115). Bergman⁵³ suggested the existence of a similar 1,4 diradical moiety (117) upon the heating of 1,6-dideuteriohexa-1,5-diyn-3-ene (116) at 300°C (Scheme 35). This type of cyclisation has been implemented as the key step in the biological mechanism of enediyne antitumour agents such as Calceamicin, where the generated *para*-benzyne abstracts protons from tumour DNA, thus preventing growth of the tumour.⁵⁴



Scheme 35

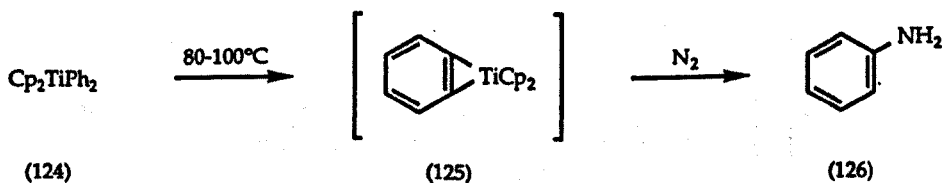
Many stable metal complexes of benzyne have been generated, but without much synthetic use, and are still awaiting exploitation in organic synthesis. For example, Zirconium complexes of benzyne have been generated *in situ*,⁵⁵ the synthesis of functionalised aromatic compounds (123), in preparatively useful yields, has been reported *via* coupling

reactions of these complexes (121) with alkenes (*Scheme 37*; $\text{Cp} = \eta^5\text{-C}_5\text{H}_5$), although whether these complexes should be considered as π -bonded benzyne or as σ -bonded *ortho*-phenylenes is debatable.⁵⁶



Scheme 37

Titanium-benzyne complexes (125) have also been generated by thermolysis of titanocene [Cp_2TiPh_2] at 80-100°C; subsequent reaction with molecular nitrogen affords anilines (126) in low yield (*Scheme 38*).⁵⁷



Scheme 38

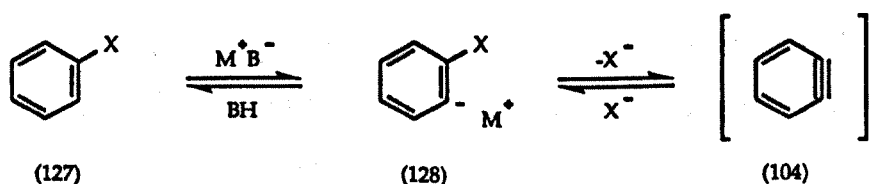
c) Approaches to Benzyne

As benzyne are intermediates that cannot be isolated due to their unstable nature, the generation and subsequent reactions of these reactive

species have to be accomplished *in situ*.^{36, 37} The methods of generation which are outlined in this chapter apply not only to the parent species, but also to various substituted benzyne, and analogous aromatic systems, examples of which are also included. Additionally, comprehensive reviews on the generation of heterocyclic analogues of benzyne have been compiled,⁵⁸ and the reader is encouraged to draw upon these reviews for a fuller account of these particular reactive intermediates; examples of pyridynes in organic synthesis have been included elsewhere in this thesis.

Via Aryl Anions

Regarded as the oldest approach to benzyne, treatment of an aromatic species (*e.g.* 127) possessing a good leaving group (X) with a strong base results in metal-hydrogen exchange at the *ortho* position to the leaving group, generating an aryl anion (128) from which the loss of either an anionic or neutral species then leads to formation of the reactive intermediate (104) (Scheme 39). Aryl halides (X = halogen) are the most widely used precursors of benzyne using this route, but a wide range of other neutral and cationic aromatic substituents have also been used.^{36, 37}

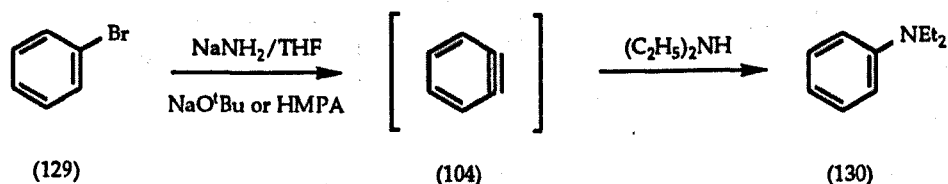


Scheme 39

As the removal of the proton and benzyne formation are reversible,⁵⁹ many factors including the nature of the leaving group, the base and solvent play important roles in benzyne formation. For aryl halides, the ease of

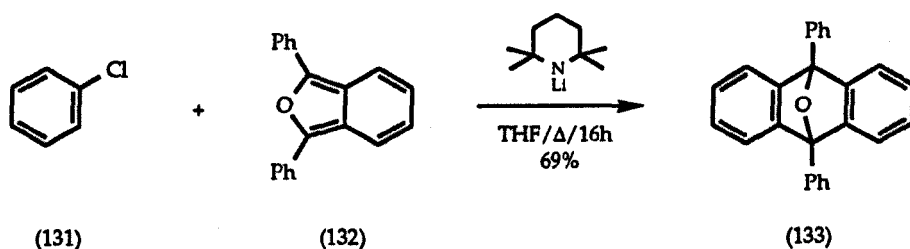
halide expulsion runs in the order $I > Br > Cl > F$, but the rates of initial proton removal are in the reverse order. In the case of fluorobenzene, proton capture competes with halide expulsion, whilst for iodobenzenes, recapture of the halide occurs easily, and consequently, chloro and bromobenzenes are used most often.

The aryl anion route to benzyne has been utilised ever since the discovery of benzyne, with Roberts⁴⁰ showing that metal amides in liquid ammonia could be used to generate *ortho*-benzyne, and Wittig³⁹ and Huisgen^{41, 60} demonstrating that metal alkyls/aryls in ethereal solvents could also be used in conjunction with the aryl halide precursor. Severe limitations of the use of these reagents arise when couplings between benzyne and weak nucleophiles are desired, as metal aryls and alkyls in aprotic solvents are very powerful nucleophiles, thus reacting with benzyne almost immediately upon their generation; even ammonia, when used as solvent is sufficiently nucleophilic to add to benzyne. Consequently, the approach from aryl halides requires some development in order to become applicable to many synthetic approaches, and one way of overcoming these problems is to use metal amides in conjunction with aprotic solvents, as these bases are adequately strong, convenient to prepare and are relatively weak nucleophiles. One example of this is the use of sodium amide in THF, which when used in conjunction with an activating compound, such as sodium *t*-butoxide or HMPA, leads to benzyne formation (104) in quantitative yield (Scheme 40).⁶¹



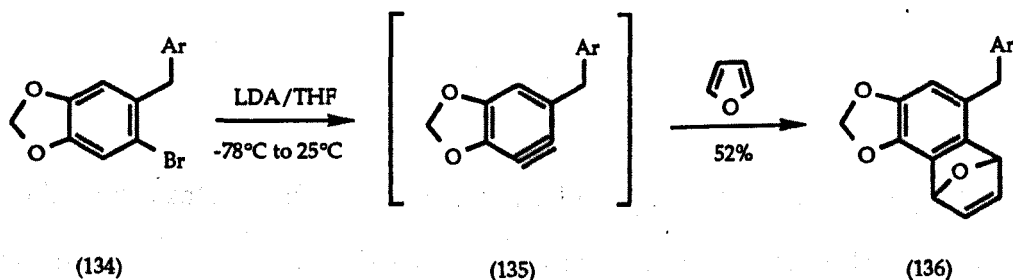
Scheme 40

In order to further minimise any reaction between benzyne and the amides, and thus improve the efficiency of benzyne-cycloaddition and benzyne-nucleophile reactions, an increasing emphasis has been placed on using more hindered amines which are unable to trap benzyne. One example is the hindered base lithium 2,2,6,6-tetramethylpiperidide [LiTMP], which has been used in conjunction with aprotic solvents to generate *ortho*-benzyne (Scheme 41).⁶²



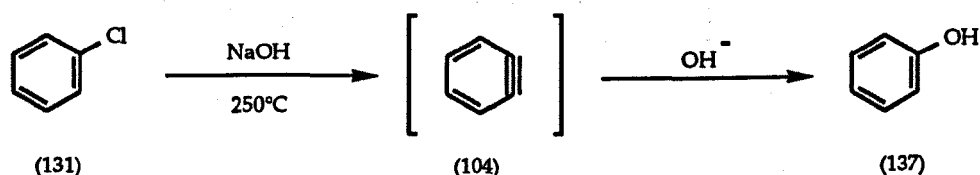
Scheme 41

A major development which has vastly improved the widespread application of the aryl anion route concerns the use of the hindered base LDA, in conjunction with THF.⁶³ Here, interaction between the benzyne and the base is minimised such that desired reactions with suitable partners can be achieved in a satisfactory manner. One example is the cycloaddition of a substituted benzyne (135), generated from the aryl bromide (134), with furan (Scheme 42).⁶⁴



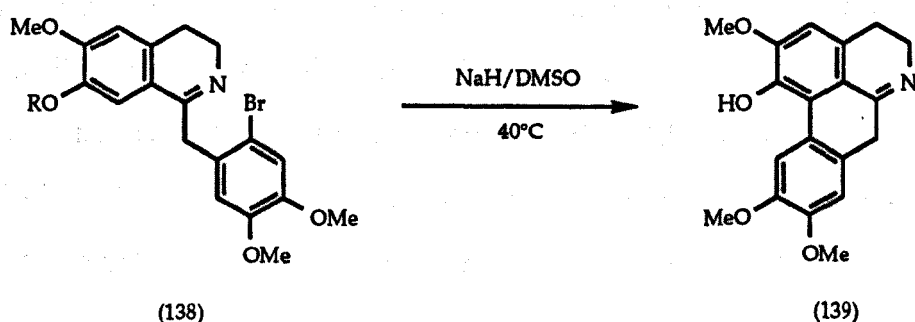
Scheme 42

Weaker bases that require higher temperatures to generate benzyne from aryl halides have also been used, though few reports on the use of such bases are to be found in the literature. One example concerns the work of Roberts *et al.*,⁴⁰ who demonstrated that sodium hydroxide reacts with chlorobenzene (131) to give phenol (137) at *ca.* 250°C (Scheme 43).



Scheme 43

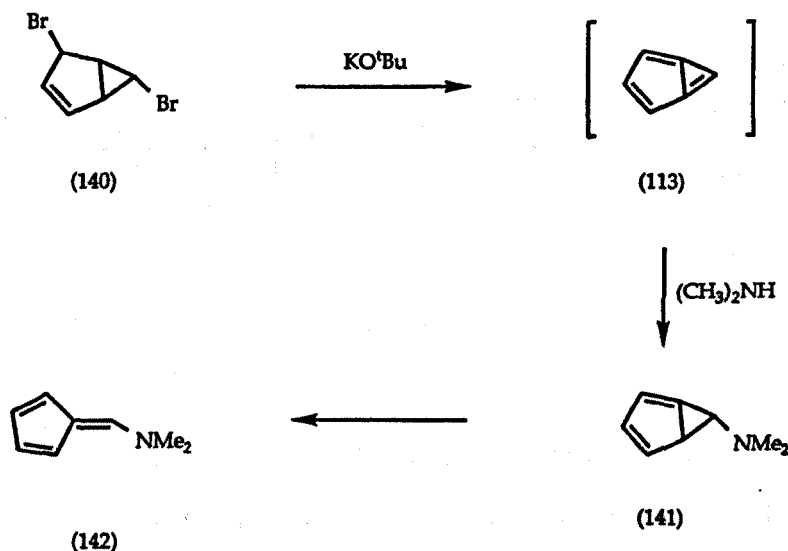
Sodium methanesulphonyl carbanions derived by the action of sodium hydride on dimethyl sulphoxide [DMSO] have been used to generate benzyne above ambient temperatures (Scheme 44).⁶⁵ Other bases that have been successfully used include potassium *t*-butoxide, either on its own,⁶⁶ or in conjunction with *t*-butyl alcohol and DMSO.⁶⁷



Scheme 44

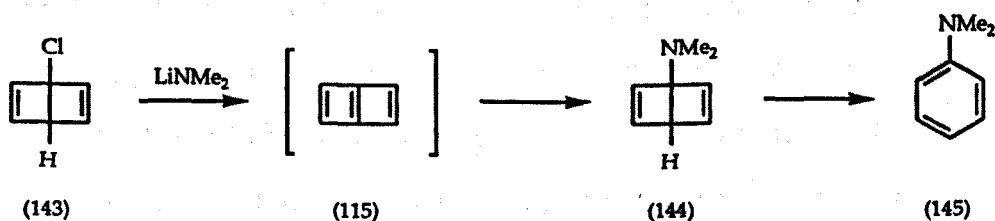
The generation of *meta* and *para*-benzyne *via* the action of strong bases on aryl halides has also been reported. For example, treatment of an appropriate bicyclic dibromide *meta*-benzyne precursor (140) with a strong

base, such as potassium *t*-butoxide, results in the formation of the bicyclic form of *meta*-benzyne (113), which can be trapped by nucleophiles such as dimethylamine to give a bicyclic intermediate (141) which ring opens to yield the final product (142) (Scheme 45).⁶⁸



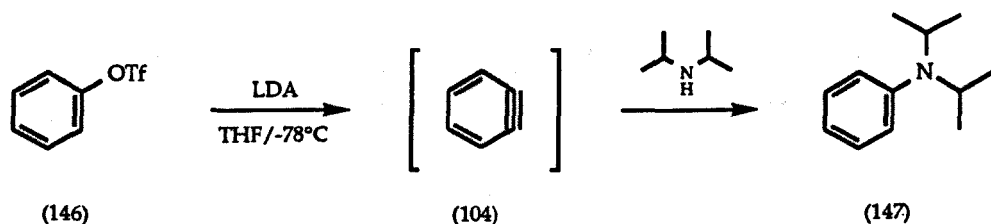
Scheme 45

Whilst the formation of *para*-benzyne has already been implicated in the cyclisation reactions of enediynes (see Scheme 35), aryl anion routes to the bicyclic forms of *para*-benzyne (115) have also been developed. These include the treatment of a bicyclic chloride (143) with lithium dimethylamide, eventually yielding dimethylaniline (145) after trapping of the reactive intermediate and rearrangement (Scheme 46).⁶⁹



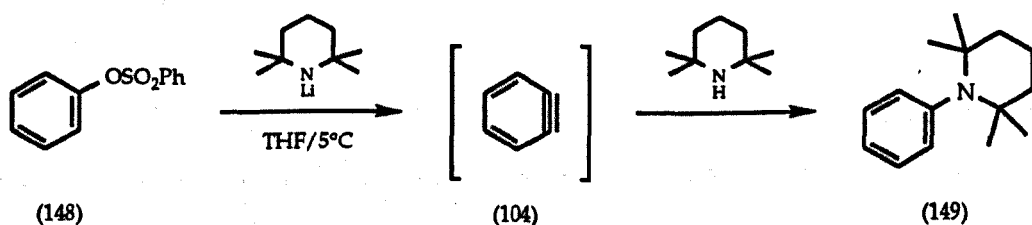
Scheme 46

Although the use of aryl halides has dominated the aryl anion route to benzyne, the use of other leaving groups has also been reported on occasions.^{36, 37} A recent example of another leaving group that has been used is the triflate group, which leads to benzyne generation (104) upon exposure to LDA in a similar manner to aryl halides (*Scheme 47*).⁷⁰



Scheme 47

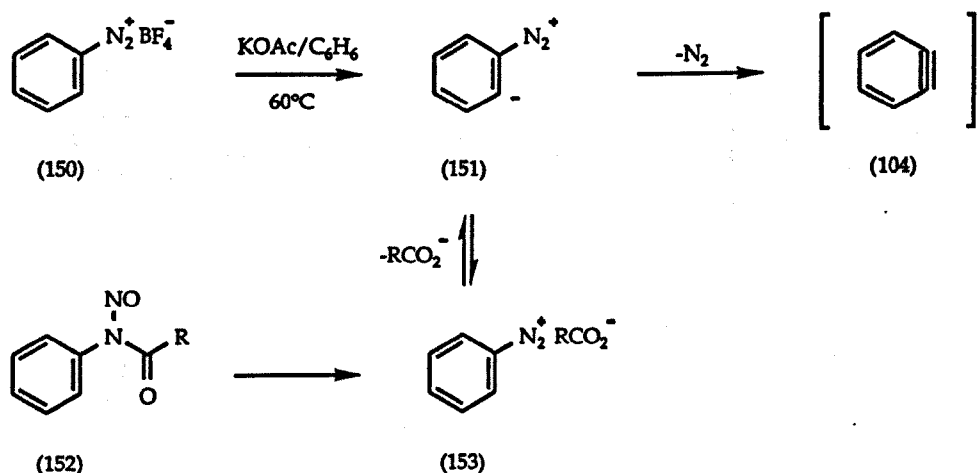
Other leaving groups which have been reported but which have seldom been used include the benzenesulphonate group (*e.g.* 148), which decomposes to the benzyne (104) upon exposure to LiTMP at low temperatures (*Scheme 48*).⁷¹



Scheme 48

Although anionic leaving groups have received much attention, neutral leaving groups have also been used, for example diazonium tetrafluoroborates (150), with benzyne generation resulting from initial proton abstraction and loss of the diazonium group.⁷² Alternatively, the betaine intermediate can be generated from *N*-nitrosoacylarylamines (152), with formation of diazonium carboxylate (153) resulting from

rearrangement of the *N*-nitroso species (Scheme 49).⁷³ In cases where a *t*-butyl substituent is *ortho* to the diazonium substituent in (150), the loss of the diazonium group is accelerated such that elimination of this group occurs prior to proton abstraction, thus providing a rare example of benzyne generation *via* an aryl cation route.⁷⁴

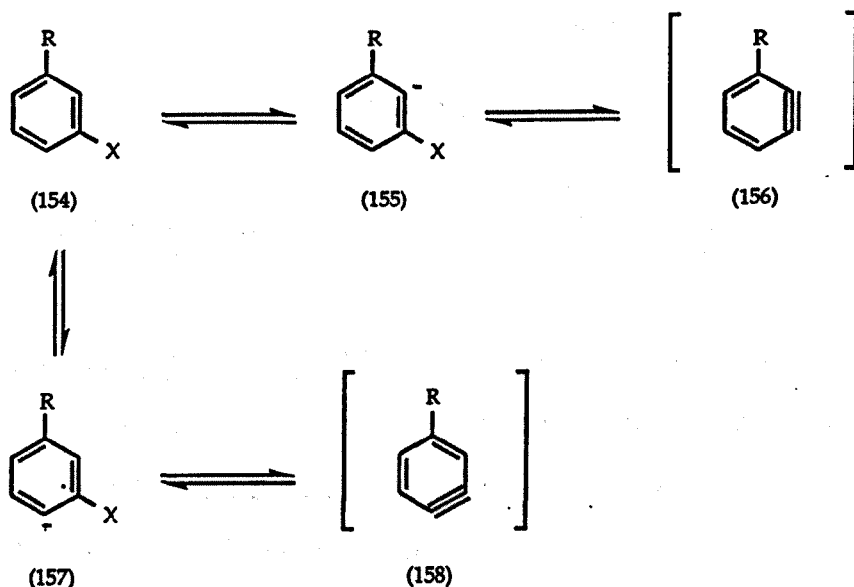


Scheme 49

Generation of Substituted Benzyne

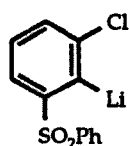
When the aryl anion route is used to generate benzyne from aryl halides, generation from *ortho* and *para*-substituted precursors is straightforward, whereas for the *meta* case, two sites of formation are possible. In these situations, regioselectivity of the site of formation depends on the relative rates and reversibility of the deprotonation and dehalogenation steps. With substituents that either exert an electron withdrawing (*-I*) effect or aid *ortho*-metallation, benzyne formation is favoured in the adjacent position, provided halide loss occurs quickly. For instance, when 3-bromoanisole (154, R = OMe, X = Br) is treated with LDA, 3-methoxybenzyne (156, R = OMe) is the major reactive intermediate

generated because the aryl anion is stabilised by the methoxy group.⁶⁴ For electron donating (+I) substituents, regioselectivity of benzyne generation is poor. For example, when 3-bromotoluene (154, R = Me, X = Br) is treated with potassium amide in ammonia, the ratio of *ortho:meta*-isomers (156:158) is 40:60 (i.e. benzyne generation proceeds along both routes in a roughly equal manner).

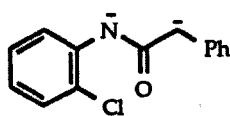


Scheme 50

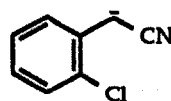
Strongly electron withdrawing substituents can stabilise the aryl anion such that halide loss fails to occur. For example, the chlorobenzene sulphonate (159) has a considerable lifetime at room temperature, whilst the corresponding bromo compound decomposes at a faster rate. Strong electron donating groups can retard deprotonation, and may stop it altogether if a negative charge is attached to the aromatic ring; for example, the anions (160) and (161) are stable towards potassium amide in ammonia, whereas for the anions (162) and (163), benzyne formation takes place,^{75, 76} thus emphasising the extent to which substituent charge delocalisation can place a delicate balance on benzyne formation.



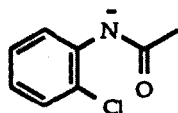
(159)



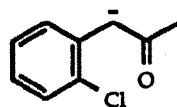
(160)



(161)



(162)



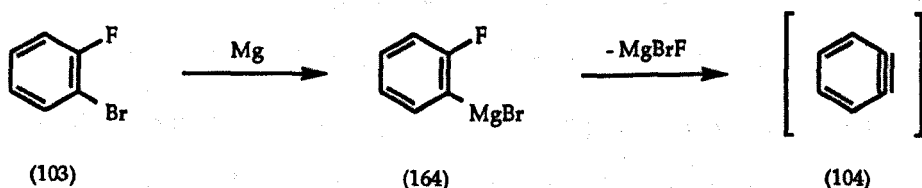
(163)

Scheme 51

Via Disubstituted Precursors

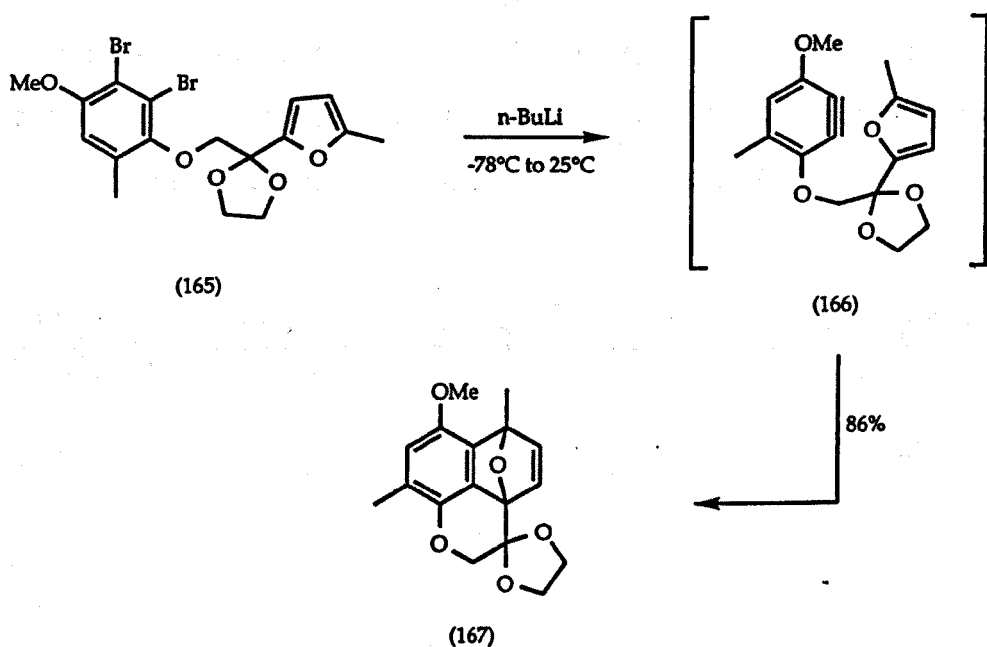
To overcome potential problems concerning ambiguity in benzyne formation from *meta*-substituted aryl anions, as outlined above (see Scheme 50), generating the benzyne using disubstituted or cyclic precursors appears to be more suitable, as the reactive triple bond can be fixed in a predetermined position.^{36, 37}

One of the most widely used disubstituted precursors are *ortho*-dihalogenobenzenes, which, upon the action of metal alkyls/aryls, lead to aryl anion formation *via* metal-halogen exchange. This method was originally developed by Wittig, who demonstrated that *ortho*-benzyne (104) could be generated from *ortho*-fluorobromobenzene (103) using either lithium amalgam (see Scheme 32) or Grignard reagents (Scheme 52).⁴²



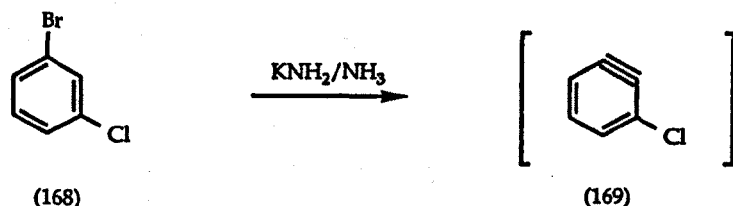
Scheme 52

This route has been modified and improved to an extent that numerous combinations of 1,2-dihalogenated precursors have been used for benzyne generation. One of the currently favoured routes of all known methods of benzyne generation concerns the use of 1,2-dibromobenzenes, in conjunction with metal alkyls such as *n*-butyllithium; this route was used by Wege⁷⁷ in the series of intramolecular Diels-Alder cycloadditions between benzyne and furans (Scheme 53).



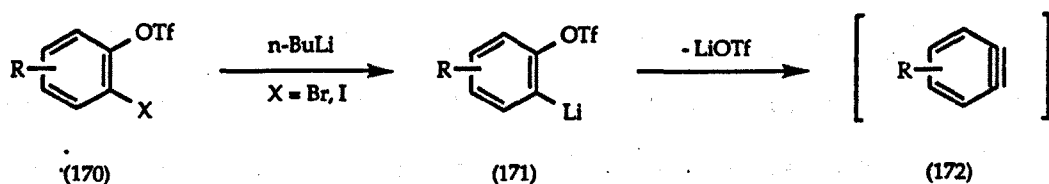
Scheme 53

Gribble *et al*⁷⁸ have shown that *meta*-substituted difluorobenzenes lead to formation of 3-fluorobenzyne *via* an aryl anion route, which is effected by the action of *n*-butyllithium at low temperatures, instead of the standard hindered base reagents (*cf.* Scheme 42). The generation of benzyne from mixed *meta*-substituted benzenes (168) has also been demonstrated by Bunnett *et al*,⁷⁹ where benzyne generation appears to occur with a degree of chemoselectivity as the bromide substituent is lost preferentially over the chloride substituent to give 3-chlorobenzyne (169) only (Scheme 54).



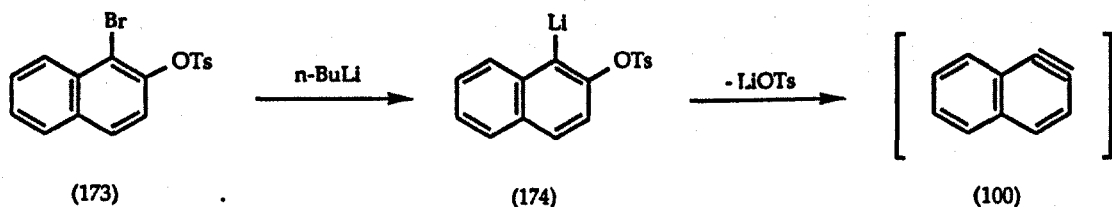
Scheme 54

Various other examples of disubstituted precursors that lead to benzyne *via* metal-halogen exchange have been reported. Suzuki *et al*⁸⁰ have recently reported that *ortho*-haloaryl triflates (170), when used in conjunction with *n*-butyllithium, lead to benzyne (172) formation in a very efficient manner *via* elimination of the triflate group (Scheme 55).



Scheme 55

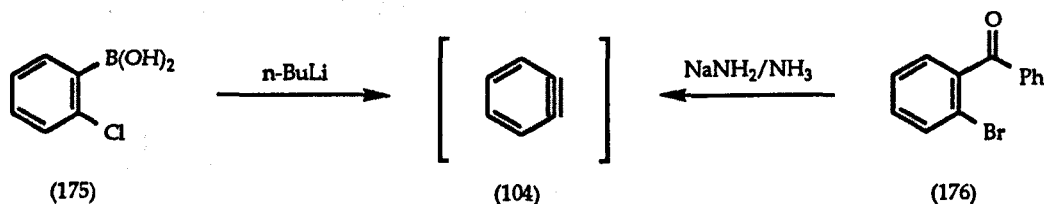
A similar aryl anion route has been reported by Tochtermann *et al*,⁸¹ who showed that 1,2-naphthalynes (100) can be generated *via* the action of *n*-butyllithium on 1-bromo-2-tosylnaphthalenes (173) (Scheme 56).



Scheme 56

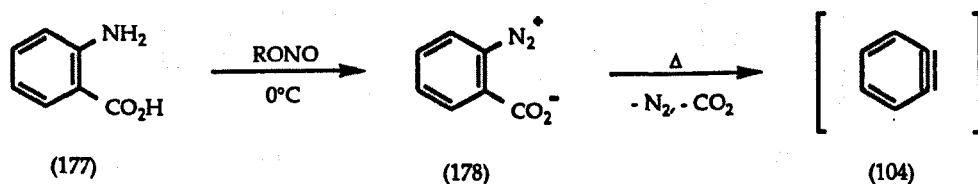
Other aryl anion-mediated disubstituted precursors which have been

reported include *ortho*-chloroaryl boronates (175), which lead to benzyne upon exposure to *n*-butyllithium. *ortho*-Bromobenzophenones (176) also lead to benzyne upon exposure to amides (Scheme 57).^{36c}



Scheme 57

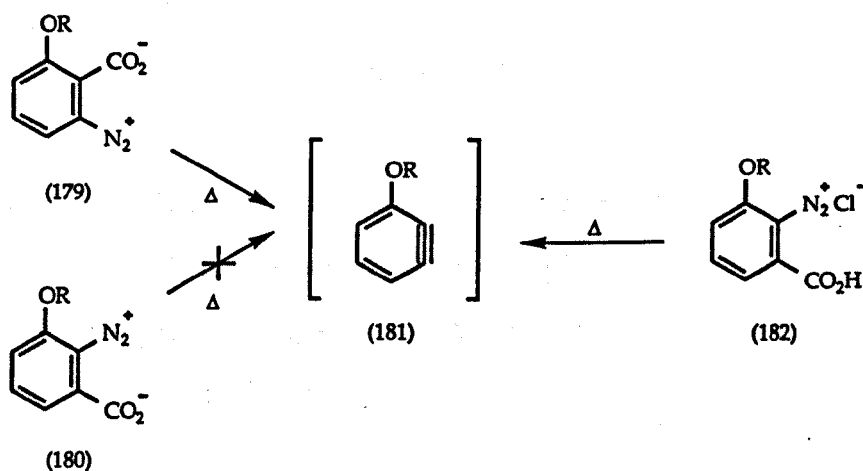
Another method of benzyne generation from disubstituted precursors concerns the collapse of zwitterionic species; the major example of this route, which is considered to be one of the classic and most popular methods of benzyne generation, concerns the decomposition of benzenediazonium-2-carboxylates.⁸² At low temperatures, anthranilic acid (177) is diazotised to give benzenediazonium-2-carboxylate (178), which decomposes upon heating in a solvent to give the benzyne (104), nitrogen and carbon dioxide. As the diazonium intermediate is extremely unstable upon isolation, generation is best achieved *in situ* using isopentyl nitrite as the reagent (Scheme 58).



Scheme 58

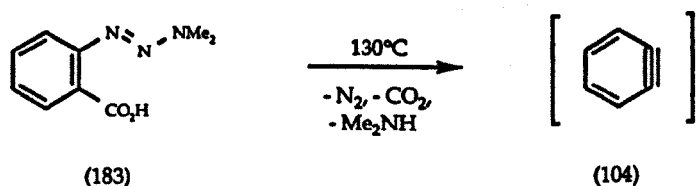
In the generation of substituted benzyne from substituted anthranilates, isomers of substituted anthranilates behave differently. Upon

heating of the 3-substituted anthranilate (179) in the presence of a suitable diene, good yields of benzyne adducts are obtained. However, under similar conditions, the anthranilate (180) produces complex mixtures (*Scheme 59*).⁸³⁻⁸⁵ Interestingly, the isolated anthranilate salt (182) does yield the benzyne (181) under similar conditions.⁸⁵



Scheme 59

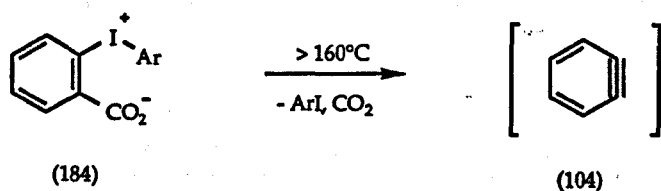
In cases where benzenediazonium carboxylates are too thermally unstable, a masked version of the diazonium group in the form of a 1,2,3-triazene (183) can be used, with decomposition being induced at high temperatures (*Scheme 60*).⁸⁶



Scheme 60

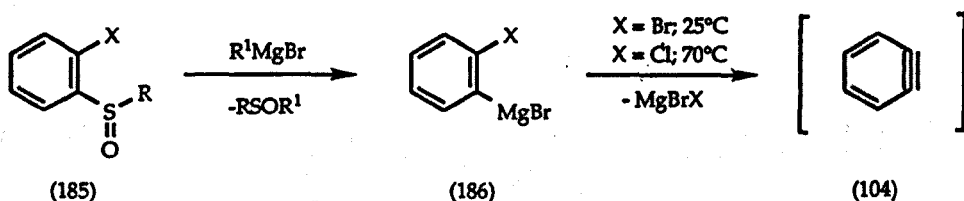
A similar zwitterionic precursor to benzyne is diphenyliodonium-2-carboxylate (184), which is more stable than benzenediazonium-2-carboxylate

and which requires temperatures above 160°C to induce decomposition (Scheme 61).⁸⁷



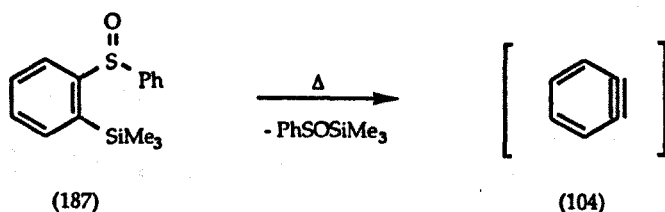
Scheme 61

Other disubstituted precursors which have received comparatively little attention include *ortho*-haloaryl sulphoxides (185) which, when treated with Grignard reagents, lead to benzyne formation *via* metal-sulphoxide exchange (Scheme 62).⁸⁸



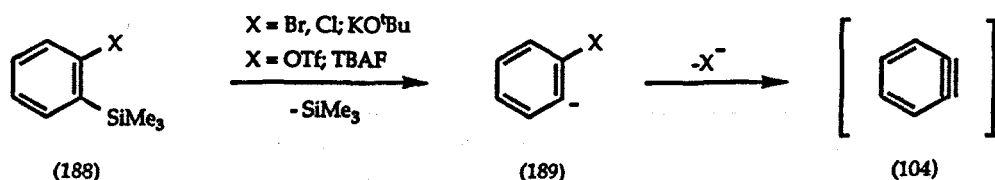
Scheme 62

Kessar^{36j} has reported that benzyne can also be generated in an analogous manner to above by heating *ortho*-trialkylsilylaryl sulphoxides (187) (Scheme 63).



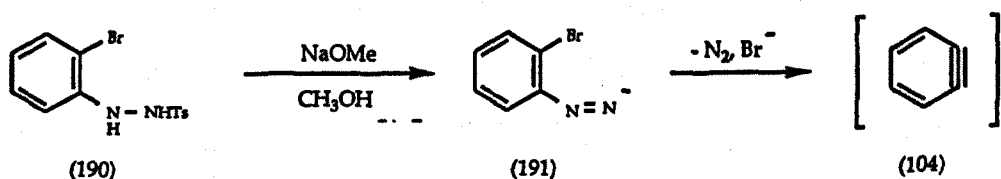
Scheme 63

Cunico and Dexheimer⁸⁹ reported the generation of benzyne *via* the action of bases on *ortho*-halophenyltrimethylsilanes (188, X = Cl, Br), whilst a Japanese group⁹⁰ have reported that aryl triflates (X = OTf) could also be used in a similar manner when exposed to fluoride reagents (Scheme 64).



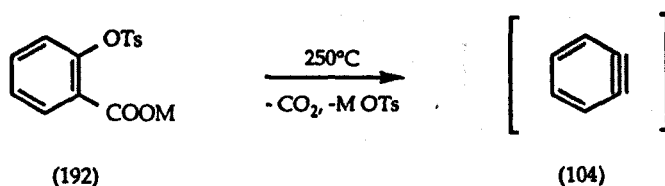
Scheme 64

Bunnett and Takayama⁹¹ have reported the formation of benzyne from the decomposition of 1-(*ortho*-bromophenyl)-2-tosyl hydrazones (190) upon exposure to weak bases such as sodium methoxide in methanol (Scheme 65).



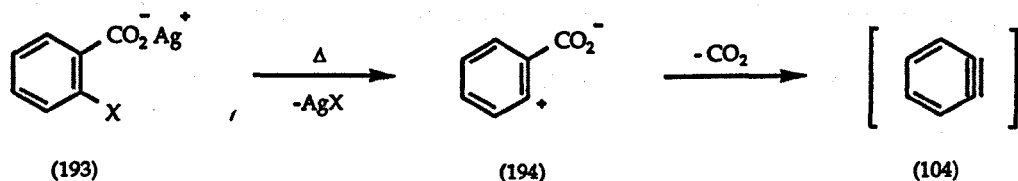
Scheme 65

Luis *et al*⁹² have also demonstrated that *ortho*-tosylbenzoates (192) ($M = \text{H, Na, K}$) decompose upon heating to high temperatures to give benzyne (Scheme 66).



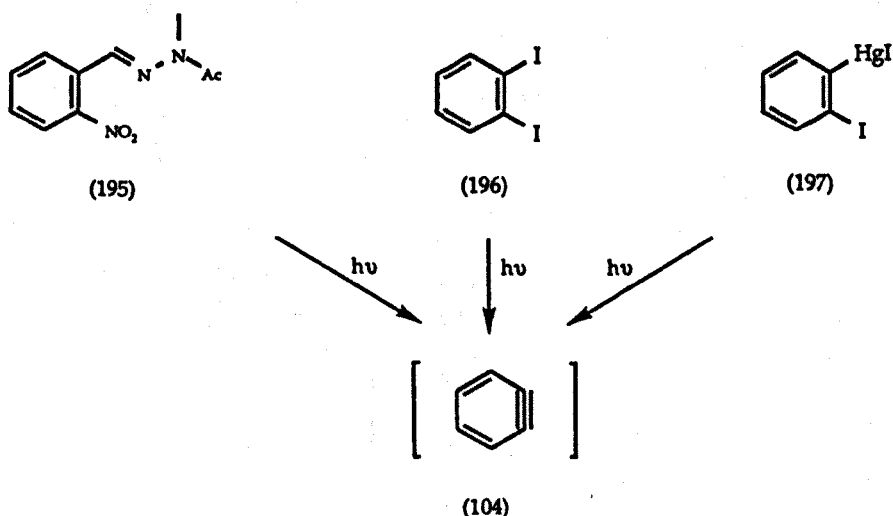
Scheme 66

The decarboxylation of *ortho*-halogenobenzoates ($X = \text{F}, \text{Cl}, \text{Br}$) represents an aryl cationic approach to benzyne, with high temperatures required for the decomposition of the *in situ* generated aryl cation (194) (Scheme 67).⁹³



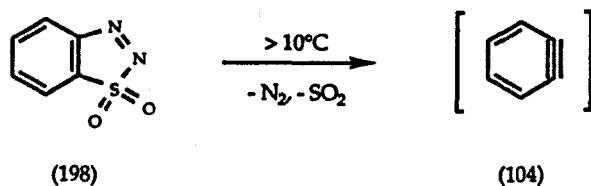
Scheme 67

Disubstituted precursors which lead to benzyne *via* other routes have been reported. The *ortho*-nitrobenzaldehyde derivative (195) yields benzyne upon irradiation,⁹⁴ as does 1,2-diiodobenzene (196)⁹⁵ (or 2-iodophenylmercury(II) iodide (197)). In the latter case, the reactive intermediate is probably generated from an aryl radical which is formed *via* cleavage of the weak C-I (or C-Hg) bond (Scheme 68). Alternatively, *ortho*-benzyne has been generated from 1,2-diiodobenzene by electroreduction.⁹⁶



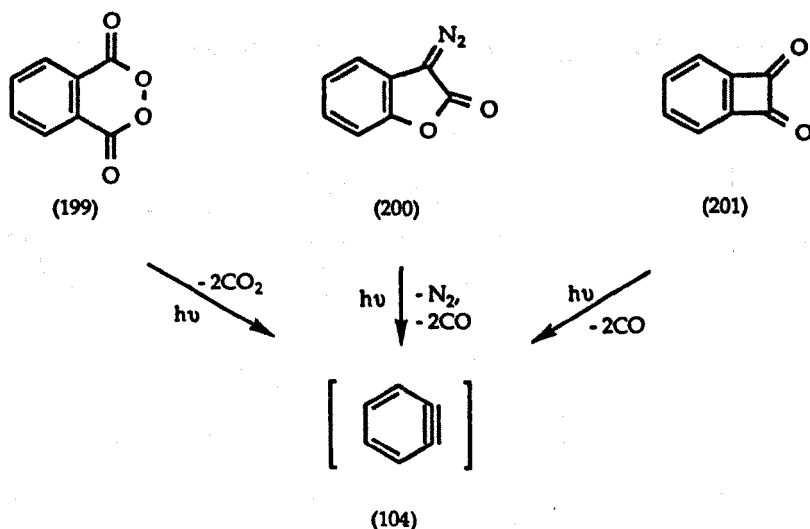
Scheme 68

The other general procedure that will ensure regioselective formation of benzyne concerns the fragmentation of benzo-fused systems that contain thermodynamically stable fragments. For instance, benzothiadiazole-S,S-dioxide (198) decomposes in organic solvents at ambient temperatures to give nitrogen, sulphur dioxide and *ortho*-benzyne (Scheme 69).⁹⁷



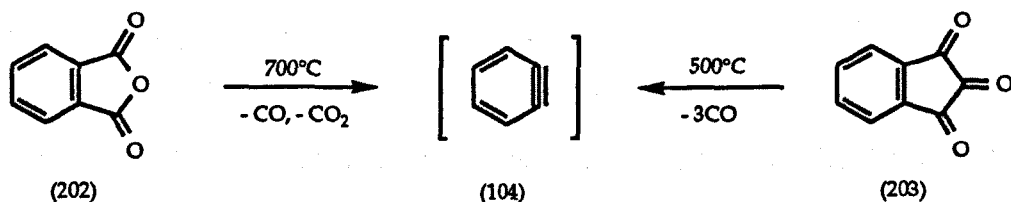
Scheme 69

Various cyclic precursors have been used to study *ortho*-benzyne at low temperatures; for example, phthaloyl peroxide (199),⁹⁸ diazalactone moieties (200), and benzocyclobutanedione (201)^{44, 99} all decompose upon photolysis to generate the reactive intermediate (Scheme 70).



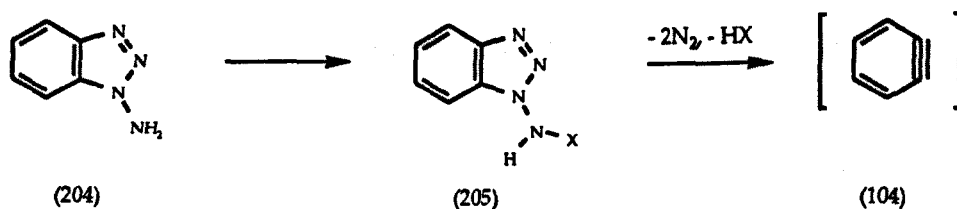
Scheme 70

Other cyclic systems exist for which the energy required to initiate fragmentation can be very high. For example, the stable species phthalic anhydride (202)¹⁰⁰ and indane-1,2,3-trione (203)¹⁰¹ both require gas phase pyrolysis for benzyne formation (*Scheme 71*).



Scheme 71

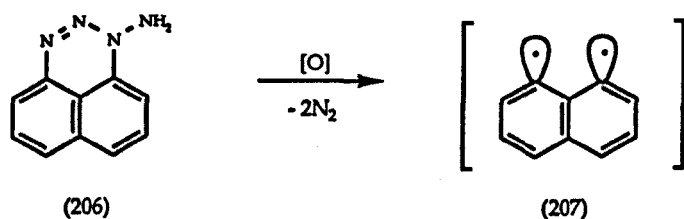
One of the most widely used cyclic precursors is the 1-aminobenzotriazole ring system.¹⁰² Here, fragmentation of the system (204) leading to the expulsion of two molecules of nitrogen and benzyne generation is triggered upon exposure to oxidising agents such as lead(IV) acetate, nickel peroxide, iodobenzene diacetate and *N*-bromosuccinimide; this can be achieved over a wide range of temperatures, even as low as -78°C. The highly efficient nature in which benzynes can be generated and subsequently used, coupled with the mild, 'neutral' conditions which are required, make this a very attractive route to benzynes (*Scheme 72*).



Scheme 72

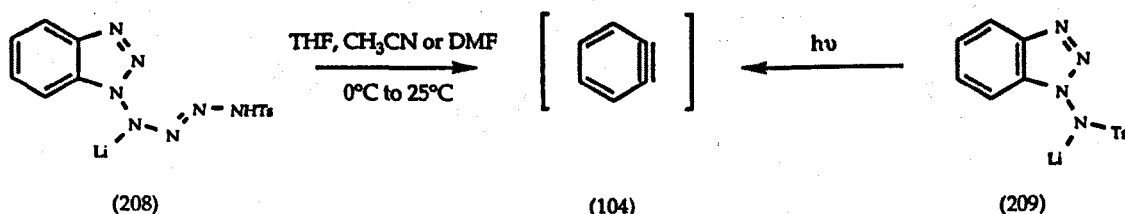
Using lead(IV) acetate as the oxidising agent, benzyne generation was originally thought to proceed through a nitrene species, but is more likely to

to proceed through an *N*-acetoxy intermediate ($X = \text{OAc}$). The unusually high yields of biphenylene obtained through the dimerisation of *ortho*-benzyne generated in this way are thought to result from a high local concentration of the reactive intermediate resulting from stabilisation *via* complexation by lead cations present in the reaction mixture. This route has also been applied to the generation of substituted benzyne, 2,3-dehydronaphthalene,¹⁰³ dehydrophenanthrene, dehydrobenzoquinone and, most notably 1,8-didehydronaphthalene (207), a 1,3-diradical form of *meta*-naphthalene (Scheme 73).¹⁰⁴



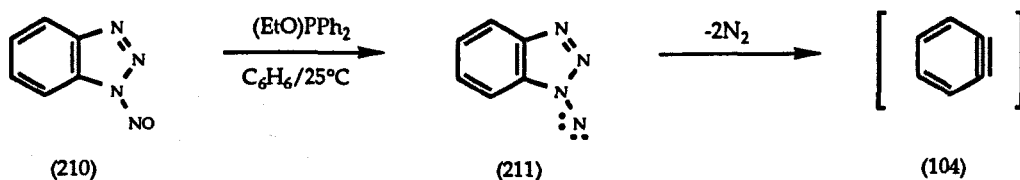
Scheme 73

Various derivatives of the 1-aminobenzotriazole ring system which avoid the use of oxidising agents have been reported. The lithium salt of 1-(benzotriazolyl)-4-tosyltetrazene (208) fragments upon addition to polar solvents at 0°C followed by warming to ambient temperature,¹⁰⁵ whilst the related species lithium 1-tosylamidobenzotriazole (209), though more stable, can be decomposed photochemically to give the reactive species (Scheme 74).¹⁰⁶



Scheme 74

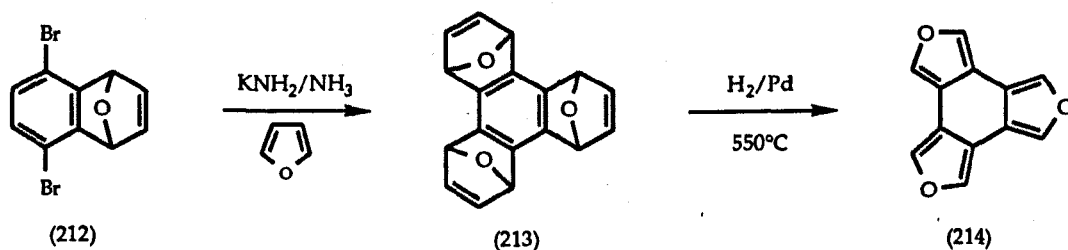
An analogous approach to the 1-aminobenzotriazole route has been reported by Cadogan and Thomson,¹⁰⁷ who showed that 1-nitrosobenzotriazoles (210) decompose to benzyne upon exposure to ethyl diphenylphosphinite at ambient temperatures, possibly *via* deoxygenation to give a nitrene intermediate (211) (Scheme 75).



Scheme 75

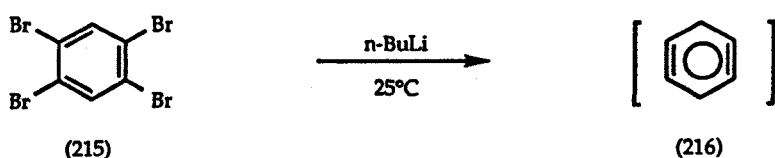
Approaches to bis-Arynes

One of the recent advances in benzyne chemistry has been the development of *bis*-arynes, where two arynic triple bonds can be formally generated in the same aromatic molecule. The first reports of such species came from Wittig¹⁰⁸ and Fields,¹⁰⁹ whilst Cadogan¹¹⁰ reported attempts to generate 1,4-benzdiynes from both 2,5-*bis*-(*N*-nitrosoacetylaryl)benzenes (*cf.* Scheme 49) and 1,4-dibromoarenes. Wege also demonstrated that 1,4-benzdiynes could be generated from 1,4-dibromoarenes (212) in the synthesis of furanyl-derived triphenylenes (*e.g.* 214) (Scheme 76).¹¹¹



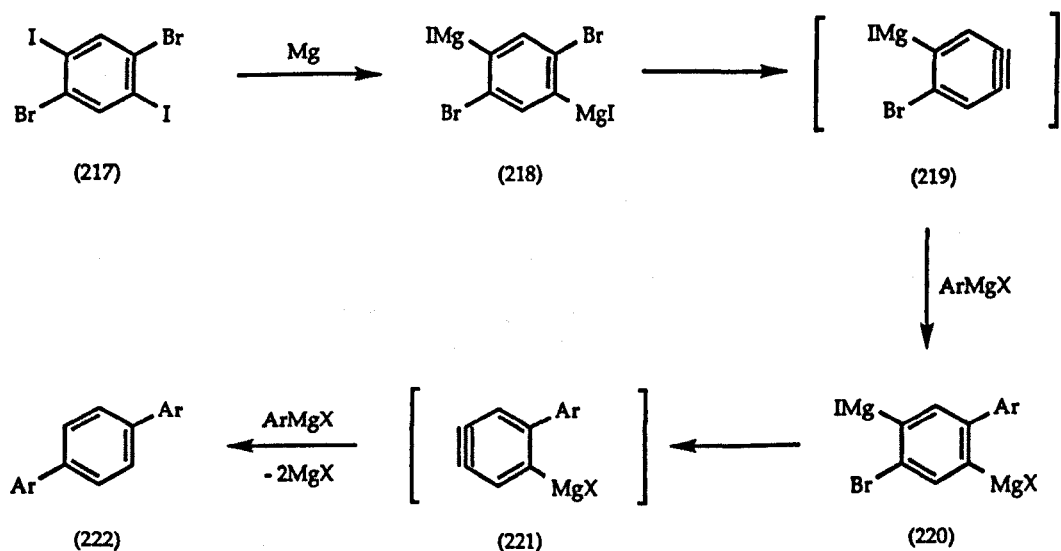
Scheme 76

Extensive studies in the development and application of *bis*-aryne equivalents to synthetic methodology have been conducted by Hart and co-workers (see also Chapters Three and Four).¹¹² The generation of 1,4-benzdiynes (216) *via* the action of *n*-butyllithium on 1,2,4,5-tetrahaloarenes has received much attention, in particular using 1,2,4,5-tetrabromobenzenes (215) (Scheme 77).¹¹³



Scheme 77

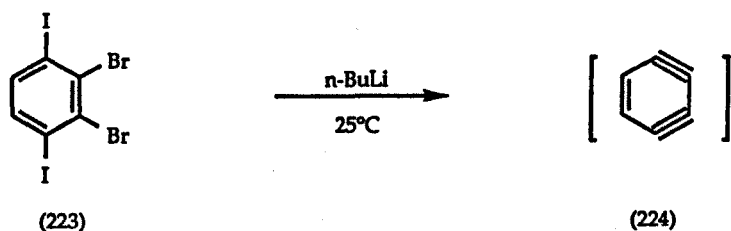
The formation of 1,4-benzdiyne equivalents from 1,4-dibromo-2,5-diiodoarenes (217) *via* the action of Grignard reagents was later reported by the same author (Scheme 78).¹¹⁴



Scheme 78

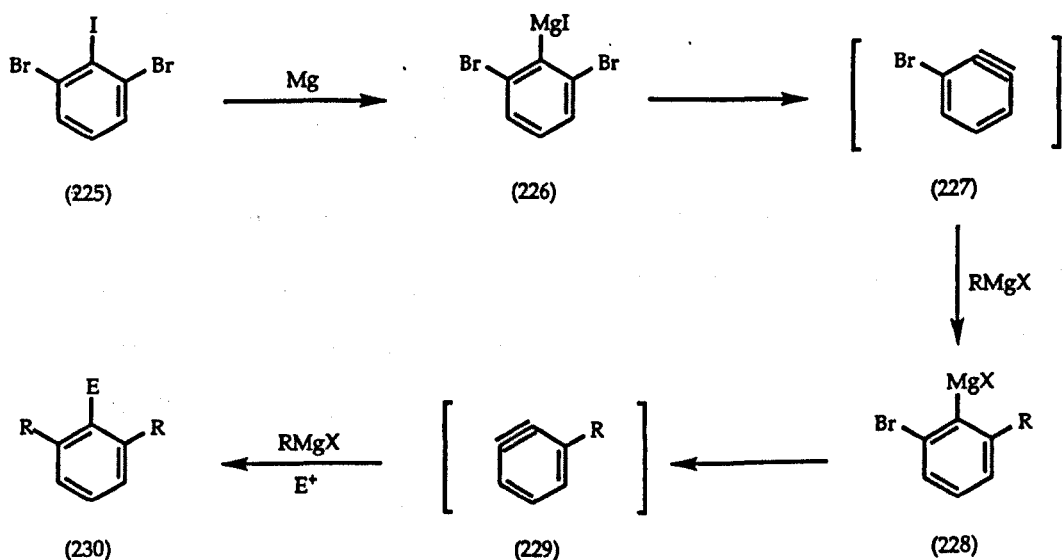
In an analogous manner to the use of 1,2,4,5-tetrahaloarenes for the

preparation of 1,4-benzdiyne equivalents, Hart has also reported the preparation of 1,3-benzdiyne equivalents (224), using 1,2,3,4-tetrahalobenzenes (e.g. 223) as precursors (Scheme 79).¹¹³



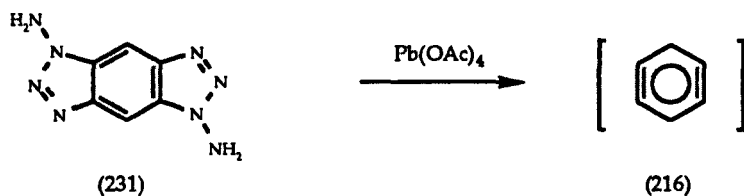
Scheme 79

Hart also described the preparation of 1,2-benzdiyne equivalents from 1,3-dibromo-2-iodobenzenes (225) *via* the action of Grignard reagents (Scheme 80).¹¹⁵



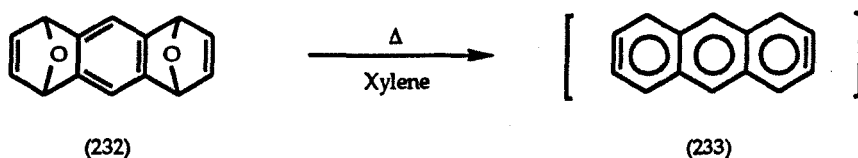
Scheme 80

A variation of the 1-aminobenzotriazole route to benzyne was later reported by Hart, where *bis*-1-aminobenzotriazoles (231) generate 1,4-benzdienes (216) upon exposure to oxidising agents (Scheme 81).¹¹⁶



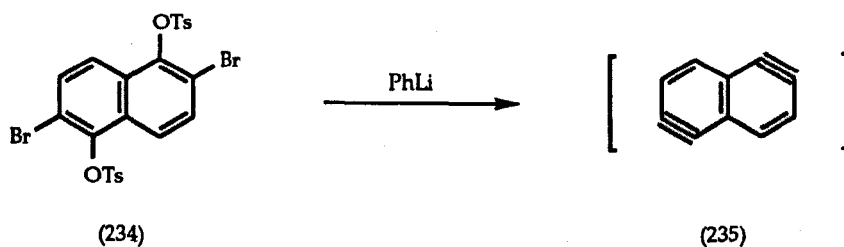
Scheme 81

In addition to the generation of benzdiynes, other forms of *bis*-arynes have been prepared. Hart¹¹⁷ reported the preparation of a 2,3,6,7-anthradiyne equivalent (233) from a diepoxytetrahydroanthracene (232) (Scheme 82), which was previously prepared from the *bis*-cycloaddition of 1,4-benzdiyne, generated from 1,2,4,5-tetrabromobenzene (215), with furan.



Scheme 82

A 1,5-naphthdiyne equivalent (235) has been reported by Gribble,¹¹⁸ where exposure of 2,6-dibromo-1,5-bis-(tosyloxy)naphthalene (234) to phenyllithium results in the preparation of this unusual reactive intermediate (Scheme 83).



Scheme 83

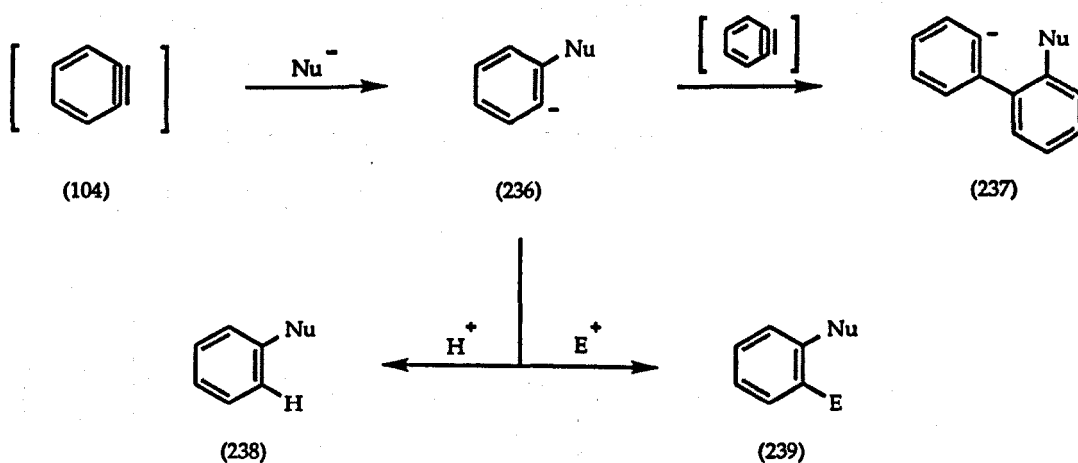
CHAPTER THREE

Nucleophilic Reactions of Benzyne

- a) Introduction*
- b) Nucleophilic Trapping of Benzyne in Organic Synthesis*

a) Introduction

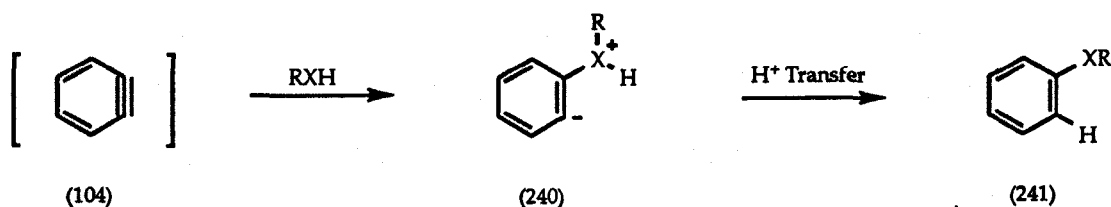
The propensity of benzyne to undergo nucleophilic attack has been evident ever since the discovery of these reactive intermediates.^{36, 37} The addition of anionic nucleophiles to *ortho*-benzyne (104) leads to the formation of either an anionic or zwitterionic intermediate (236), which can undergo several different reactions, depending on both the nucleophile involved and the conditions under which the benzyne is generated (Scheme 84). The intermediate can then either add to further molecules of the benzyne to give polymeric products (e.g. 237), or, in acidic media, it can pick up a proton, *via* either abstraction from the surroundings or an internal rearrangement to give monosubstituted products (238). Alternatively, the intermediate can be quenched by suitable electrophiles to give 1,2-disubstituted products (239).



Scheme 84

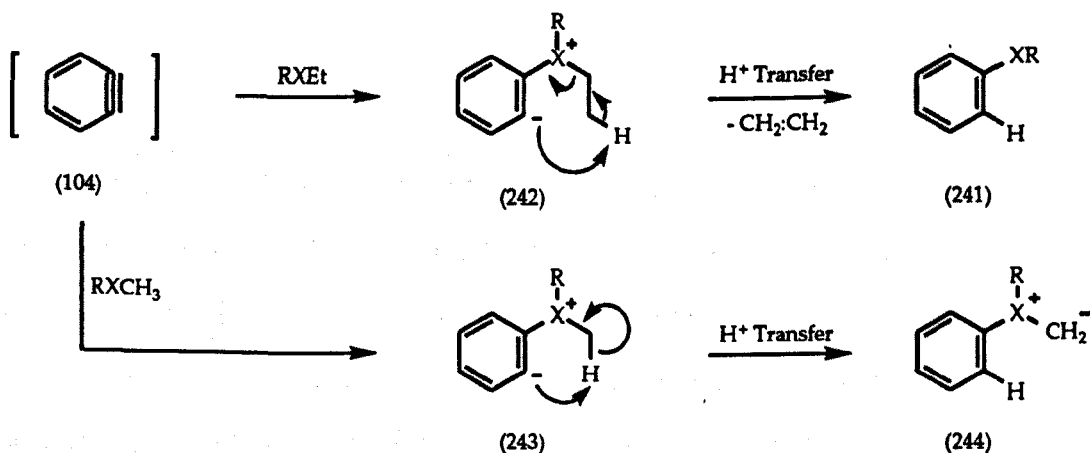
Uncharged molecules of the type RXH that possess a nucleophilic heteroatom (X) (such as water, carboxylic acids, alcohols, thiols, primary and secondary amines) add readily to benzyne, in some cases exhibiting

reactivity comparable to anionic nucleophiles. The product (241) is generated by a two-step process where zwitterion formation (240) is followed by proton transfer from the nucleophile (Scheme 85).



Scheme 85

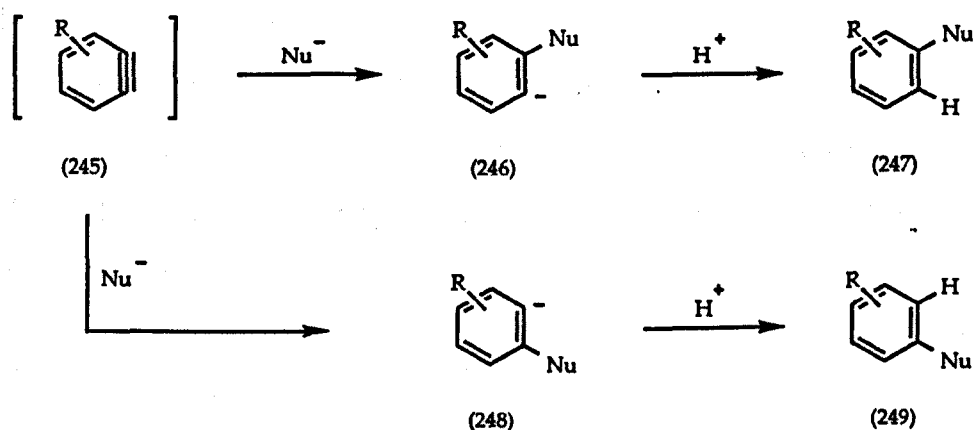
For the addition of aprotic nucleophiles (such as tertiary amines, dialkyl sulphides, ethers, phosphines or phosphites), proton transfer leading to product formation cannot be achieved. Instead, the zwitterion can undergo a rearrangement, depending upon the nature of the attacking nucleophile; if the heteroatomic nucleophile possesses a β -hydrogen such as in intermediate (242), then a proton shift *via* a betaine elimination can result to give product (241). If no β -hydrogen is present but α -hydrogens are, as in intermediate (243), then proton transfer may occur, leading to the formation of a ylide species (244).



Scheme 86

For unsymmetrical benzyne (*e.g.* 245), nucleophilic attack can occur at either end of the triple bond to give two potential products (247) and (249), and, as a consequence, the aromatic substituents can play a vital role in the site of attack, mainly through electronic effects, and to a lesser extent through steric effects. The nucleophilicity of the reagent can also play a role in this selectivity, as stronger nucleophiles tend to be less selective.¹¹⁹

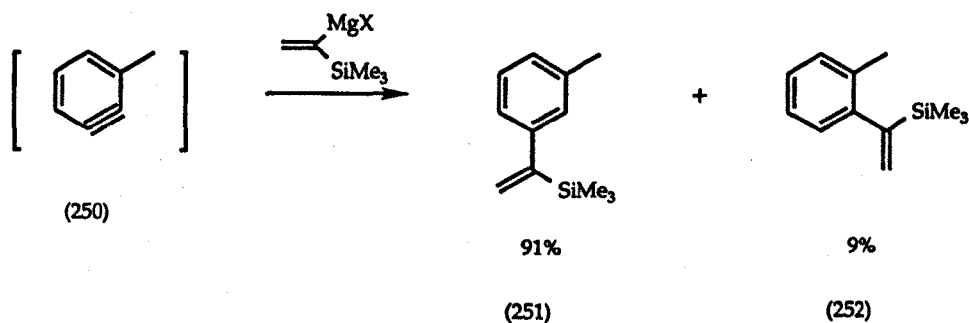
As the reactive triple bond is orthogonal to the π -system of the aromatic ring, electronic effects of substituents can only be relayed through the σ -bond framework of the ring system *i.e.* inductive effects play more of a role than mesomeric effects. These effects can influence the site of attack by the polarisation of the third bond, or by stabilisation/destabilisation of the negative charge in the transition state (246) and (248).



Scheme 87

In the case of 3-substituted benzyne, if the benzyne possesses electron withdrawing ($-I$) substituents, then the negative charge in the transition state resulting from addition at the *meta* site (248) can be stabilised through inductive effects, leading to significant regioselectivity in the final product, favouring the formation of compound (249). On the other hand, if electron donating ($+I$) substituents are present, then the inductive and steric effects

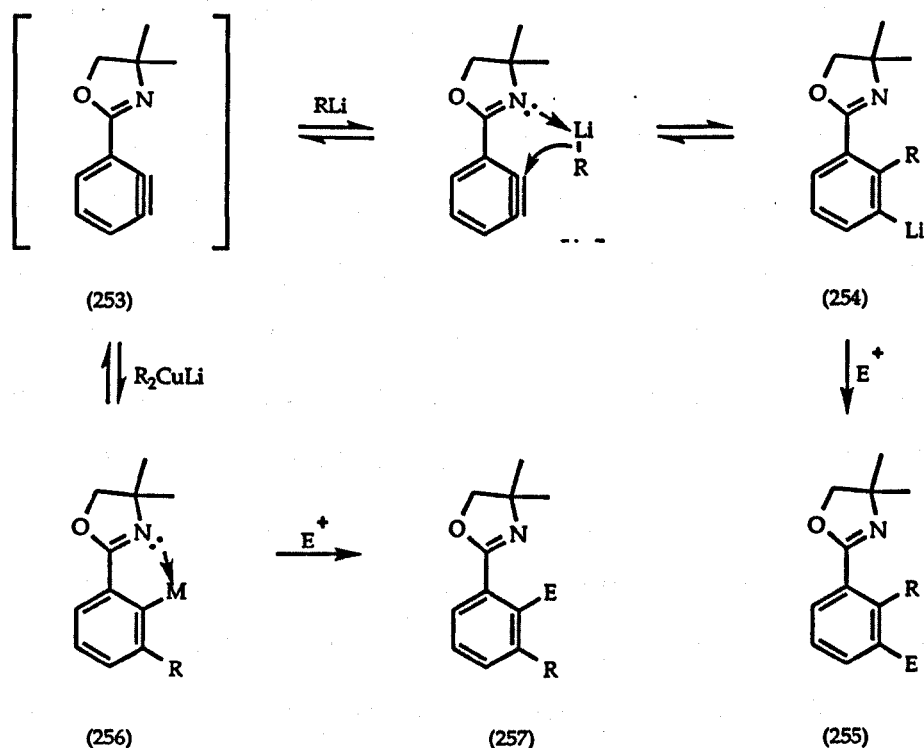
may work in opposition to each other, as *ortho* addition of the nucleophile may not lead to a less destabilised intermediate, but instead one that is more congested (e.g. 246). High regioselectivity in favour of *ortho* addition can only be effected if the substituent is a powerful electron releasing group,¹²⁰ thus destabilising the intermediate (248) generated *via meta* addition relative to the substituent. For weak electron releasing groups such as methyl groups, addition tends to occur equally at both sites, and regioselectivity is dependent on the steric bulk of the substituent. When bulky substituents or nucleophiles are involved, steric effects come into play; for example, the addition of lithium piperidide to 3-isopropyl benzyne results in an *ortho:meta* ratio of 1:24, whereas for 3-methylbenzyne the ratio is 1:2. For the addition to 3-methylbenzyne by KNH_2 and KNPh_2 , the bulkier nucleophile adds exclusively to the less hindered *meta* site, whereas the less hindered base adds to both sites in roughly equal amounts. This trend of regiospecific *meta* addition using bulky nucleophiles has been applied by Hart¹²¹ to the preparation of *meta*-substituted toluenes, where attack of the Grignard reagent predominates at the *meta* site to give compound (251) (Scheme 88).



Scheme 88

Control of nucleophilic addition to 3-substituted benzyne by complexation between substituents and incoming nucleophiles possesses

considerable potential for the regioselective formation of products, though it remains rather unexploited. One such example includes the addition of organometallic reagents to benzyne, where complexation between the substituent and the organometallic reagent can direct the incoming group into the *ortho* position, thus inducing some degree of control over the site of substitution. In the addition of alkyllithiums to benzyne possessing oxazolinyl substituents,¹²² complexation of the nucleophile by the substituent leads to the *ortho*-substituted product (255) only, which can be attributed to kinetic control. In contrast, when lithium dialkylcuprates are used in the same process, the more ligated and stable adduct (257) is formed *i.e.* thermodynamic control of the reaction leads to formation of the *meta*-substituted product (Scheme 89).



Scheme 89

For nucleophilic attack onto 4-substituted benzyne, both inductive and

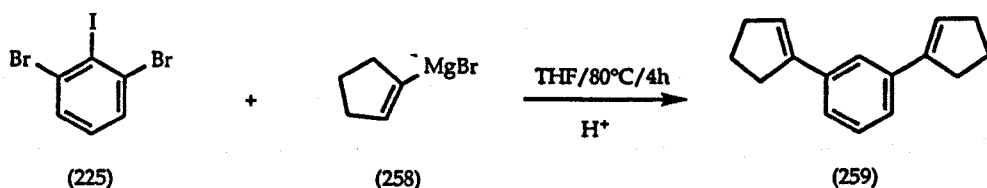
steric effects are much reduced compared to similar 3-substituted cases because of the greater distance between the substituent and the reactive intermediate. Consequently, addition generally occurs equally at the two possible sites. This is illustrated in the *meta:para* ratio of products from the addition of lithium piperidide to 4-methylbenzyne and 4-methoxybenzyne, where the ratio of products is roughly equal, compared to that for 3-methylbenzyne and 3-methoxybenzyne, where the ratios are 1:2 and 5:95 respectively.^{36d} One particular example of high *meta:para* regioselectivity concerns the addition of aryl Grignard reagents to polyhalogenated arenes (see *Scheme 78*),¹¹⁴ where the pronounced selectivity in the addition was attributed to the necessity of keeping the two negative charges away from each other.

b) Nucleophilic Trapping of Benzyne in Organic Synthesis

Although it has been long established that benzyne are considered to be highly electrophilic species, several factors have prevented these reactive species from being widely exploited in nucleophilic-based reactions.^{36, 37, 123} Firstly, considerable effort is usually required for the construction of suitable benzyne precursors. Additionally, in most cases, the requirement of nucleophilic derived reagents, and basic conditions, for benzyne generation from these precursors results in interference with the desired reactions. Finally, the extremely unstable nature of benzyne also leads to their desire to take part in various other side reactions. With the onset of non-nucleophilic reagents for benzyne generation, however, as mentioned in Chapter Two, the opportunity for increasing the utility of benzyne in nucleophilic reactions appears to have increased in recent years. Outlined in the rest of this chapter are some of the ways in which benzyne have been put to synthetic use in such reactions.

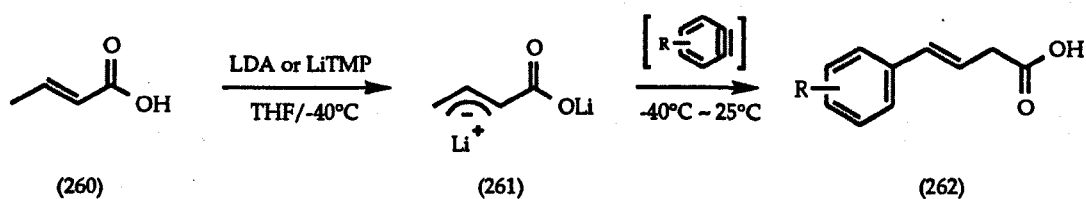
Intermolecular Trapping of Benzyne

The use of intermolecular trapping of benzyne in organic synthesis surfaces in various guises, with the simplest being the preparation of substituted aromatic compounds *via* addition of anionic nucleophiles. The extensive work of Hart on the generation of 1,3- and 1,4-benzdienes from polyhalobenzenes has been applied by the same author to the preparation of *ortho*, *meta* and *para*-terphenyls (e.g. 222; Scheme 78),^{114, 115} highly substituted aromatic compounds which are otherwise difficult to prepare, *via* the sequential trapping of the reactive intermediates by aryl Grignard reagents. Hart has also reported the synthesis of other highly substituted benzenes using alkenyl and alkynyl Grignard reagents,¹²⁴ for example in the preparation of (arylalkenyl)silanes (251; Scheme 88),¹²¹ and in the synthesis of 1,3-bis-(1'-cycloalkenyl)benzenes (259) *via* a tandem sequence starting from 1,3-dibromo-2-iodobenzene (225) (Scheme 90).¹¹⁵



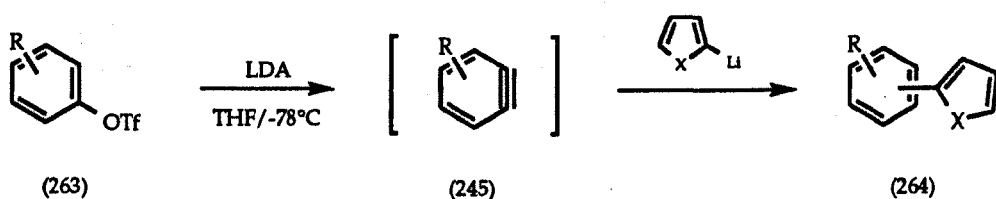
Scheme 90

The construction of 4-aryl-3-butenic acids (262) *via* the condensation of the dianion (261) generated from 2-butenic acid (260) with substituted benzyne has been recently reported by Biehl,¹²⁵ with minor quantities of the 4-aryl-2-butenic acid also being formed during the course of the reaction (Scheme 91). The exclusive 4-addition of the dianion, instead of the normally predominant 2-addition, was effected by conducting the reactions at low temperatures.



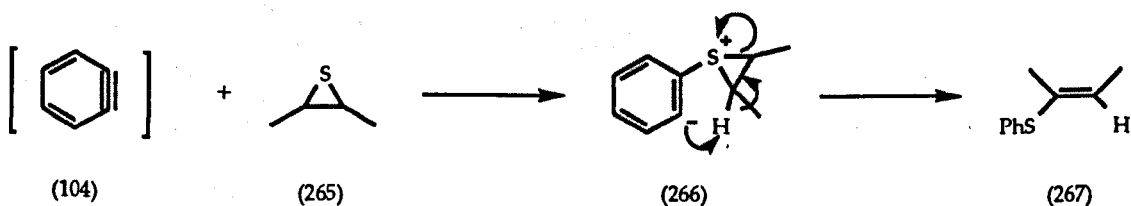
Scheme 91

Another recent example of arylation concerns the synthesis of 2-aryl furans (264) *via* the trapping of substituted benzyne (245) by heteroaryllithiums (X = O, S), where the ratio of *cine* and *ipso*-substituted products depends on the substituent effects in the benzyne (Scheme 92).¹²⁶



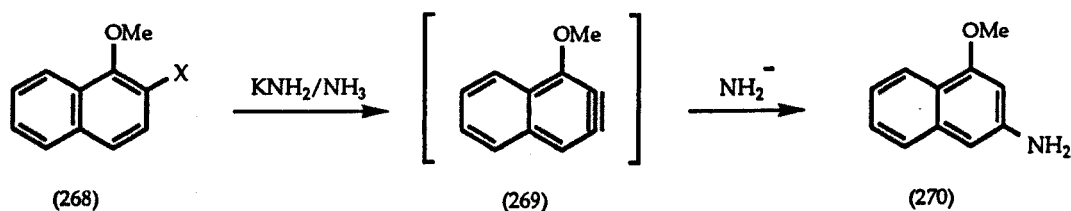
Scheme 92

The addition of uncharged heteroatomic nucleophiles to benzyne has also been exploited in organic synthesis, although to a limited extent.¹²³ One particular example concerns the addition of thi-iranes (265) to *ortho*-benzyne (104), and the subsequent rearrangement of the zwitterionic intermediate (266) leading to the synthesis of phenyl vinyl sulphides (267) (Scheme 93).¹²⁷



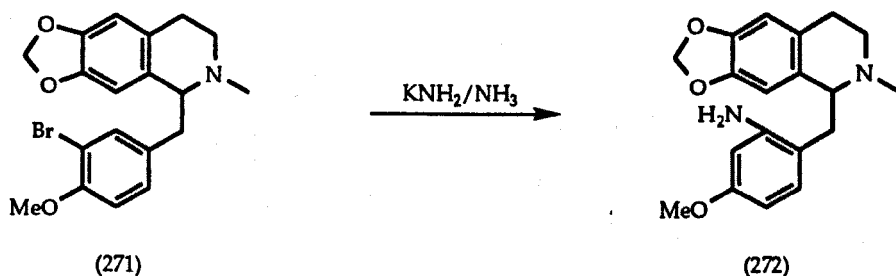
Scheme 93

cine-Substitution resulting from nucleophilic addition to benzyne has been exploited in the preparation of a variety of unusually substituted aromatic compounds, which are otherwise difficult to prepare. One previously mentioned example is the use of 3-oxazoliny benzyne for the introduction of substituents (see *Scheme 89*), whilst another example below illustrates how treatment of methoxyhalogenated naphthalenes (268) with potassium amide in liquid ammonia leads to formation of 3-methoxynaphthaniline derivatives (270) *via* the *meta*-addition of the amide anion (*Scheme 94*); conventional routes to methoxynaphthanilines lead only to the formation of the *ortho*-isomer.¹²⁸



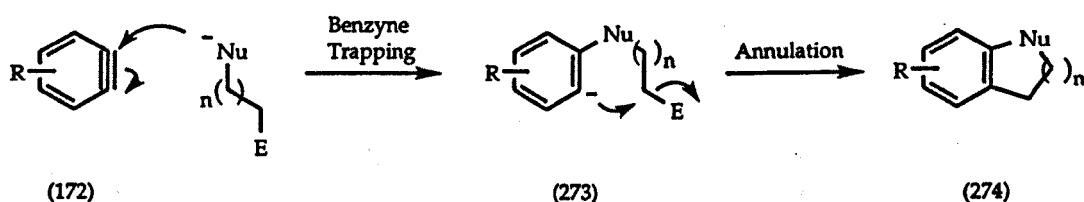
Scheme 94

cine-Substitution has also been applied to natural product synthesis. For example, in the synthesis of the alkaloid Laureline, formation of the key intermediate 3-methoxyaniline (272) is accomplished by treatment of the bromide (271) with potassium amide, and subsequent trapping of the reactive intermediate by residual amide anions (*Scheme 95*).¹²⁹



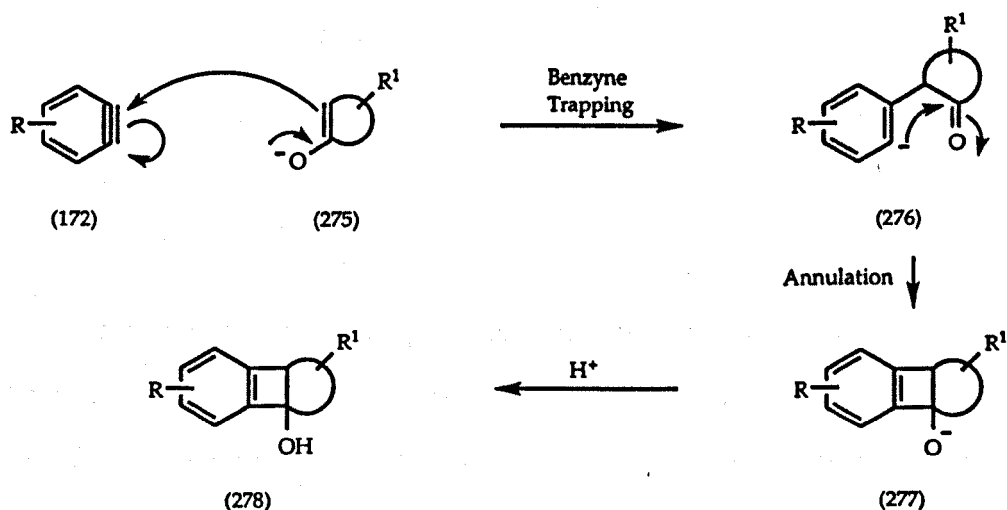
Scheme 95

One of the major synthetic applications of the intermolecular nucleophilic trapping of benzyne concerns the construction of polycyclic ring systems.¹²³ Two general methods have been developed in this area, the first of which utilises the bifunctional nature of benzyne; if the attacking nucleophile carries a suitable electrophilic centre (or a masked electrophilic centre to be unmasked during addition), then the *in situ* generated aryl anion in intermediate (273) may attack the electrophilic site to complete an overall annulation process (Scheme 96).



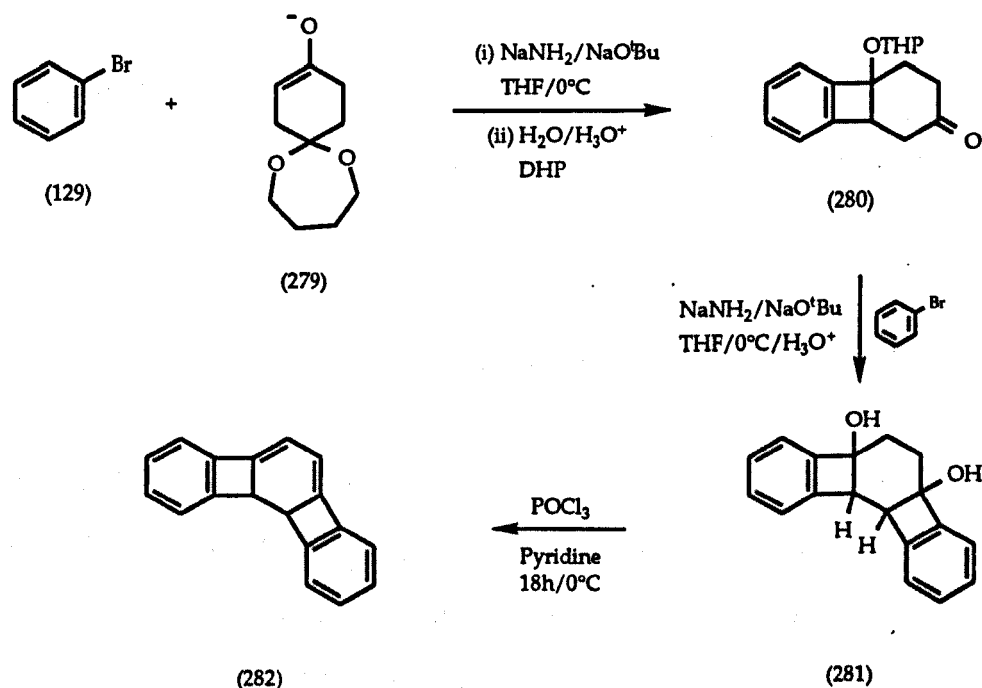
Scheme 96

Caubere demonstrated that benzocyclobutenols (278) could be prepared *via* the trapping of benzyne (172) with enolates (275) derived from five, six and seven-membered cyclic ketones (Scheme 97).^{61b}



Scheme 97

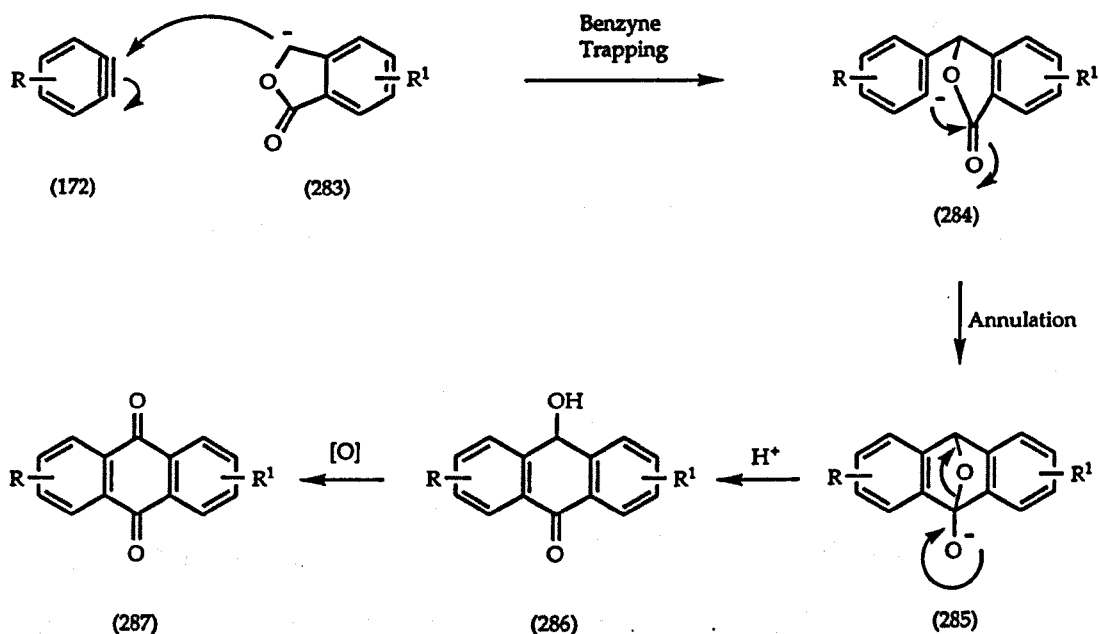
Caubere later showed how these benzocyclobutenols could be formed using enolates derived from both linear aliphatic and alicyclic diketone monoketals,¹³⁰ and that under basic conditions, the preparation of benzocyclenone and indanone derivatives from products such as (277) could be achieved by undergoing subsequent rearrangement and ring expansion.¹³¹ The same author later extended his studies to the condensation of 3,4-pyridynes with cyclic ketones,¹³² and in the synthesis of benzocyclobutabiphenylenes (e.g. 282) which are thought to possess antitumour and antiviral activity (Scheme 98).¹³³



Scheme 98

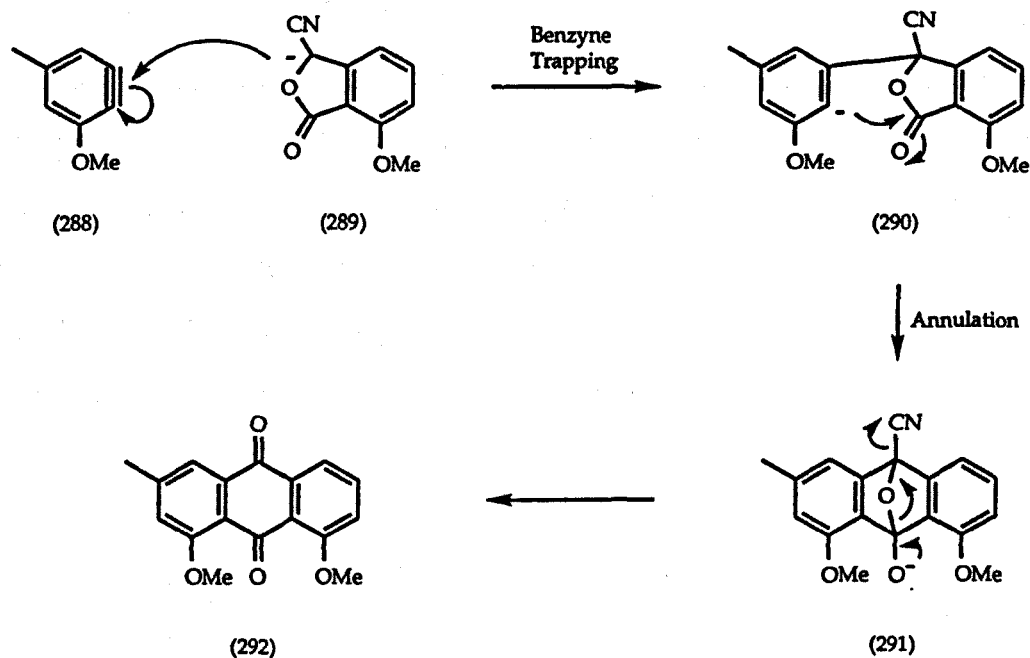
One of the main natural product targets for this area of annulative chemistry is the anthraquinone ring skeleton, which is common to many compounds possessing some form of biological activity. Sammes *et al* have described the synthesis of a number of anthraquinones (287) by treating substituted benzyne (172) with lithiated phthalides (283), with ring opening

of the hemiacetal (285) leading to the formation of a 10-hydroxyanthrone (286) which is oxidised in air to give the anthraquinone skeleton (Scheme 99).¹³⁴ Townsend later extended this methodology to the synthesis of intermediates in Aflatoxin B₁ biosynthesis.¹³⁵



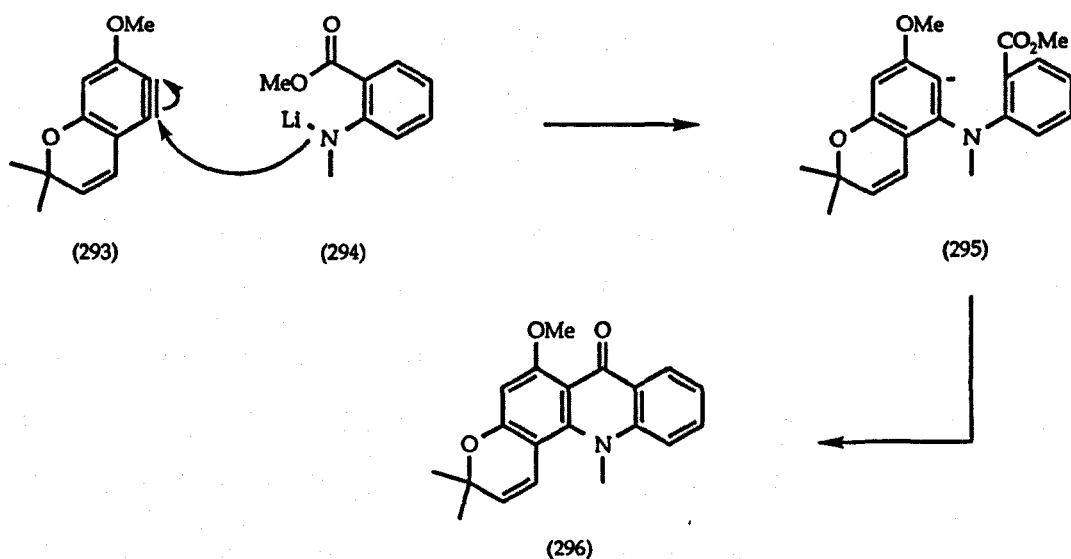
Scheme 99

Russell and Warrener¹³⁶ have shown that lithiated 3-(phenylsulphonyl)phthalides can be used to obtain anthraquinones **without** requiring the oxidation step. Biehl *et al* have also reported the synthesis of these ring systems without the requirement of an oxidation. This was accomplished by treating substituted benzynes (288) with lithiated 3-cyanophthalides (289), with the cyano hemiacetal (291) being directly converted to the corresponding anthraquinone (292) (Scheme 100). The same author has applied this route to the synthesis of naturally occurring anthraquinones, aza-anthraquinones (resulting from condensations involving 3,4-pyridynes), and tetracyclic anthracyclinones, by using annulated benzynes.^{123c}



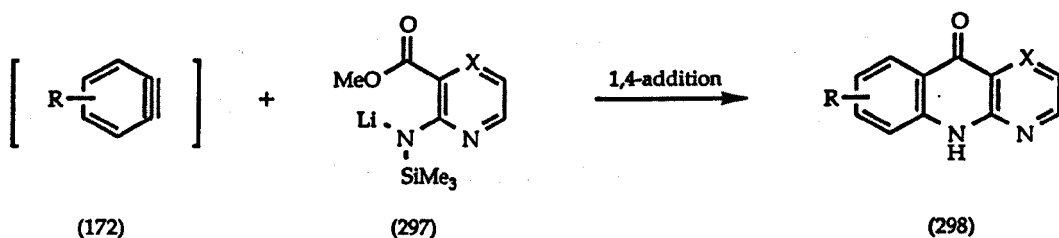
Scheme 100

A similar annulative process has been reported by Watanabe *et al*, who demonstrated that acridones such as Acronycine (296) can be obtained *via* the 1,4-dipolar cycloaddition of lithiated *N*-methyl anthranilic acid esters (294) to a substituted benzyne (293) (Scheme 101).¹³⁷



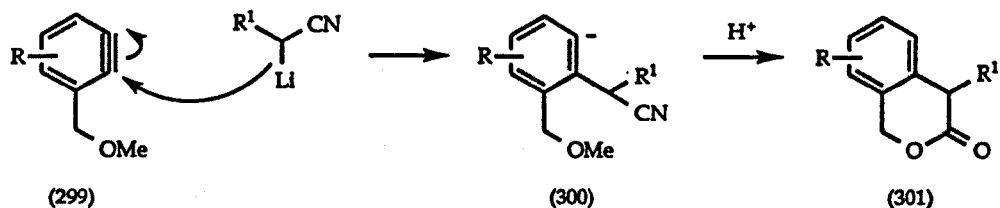
Scheme 101

Biehl has also conducted studies into the synthesis of symmetrical acridones by a 1,4-dipolar cycloaddition process *via* the trapping of lithiated *N*-methyl anthranilite esters with substituted benzyne.¹³⁸ The same author later reported that unsymmetrical benzyne (172) will undergo 1,4-dipolar cycloaddition with aminotrimethylsilylnicotinate (X = C) and aminotrimethylsilylpyrazine (X = N) esters (297), leading to the formation of acridones and aza-acridones (298) (Scheme 102).¹³⁹



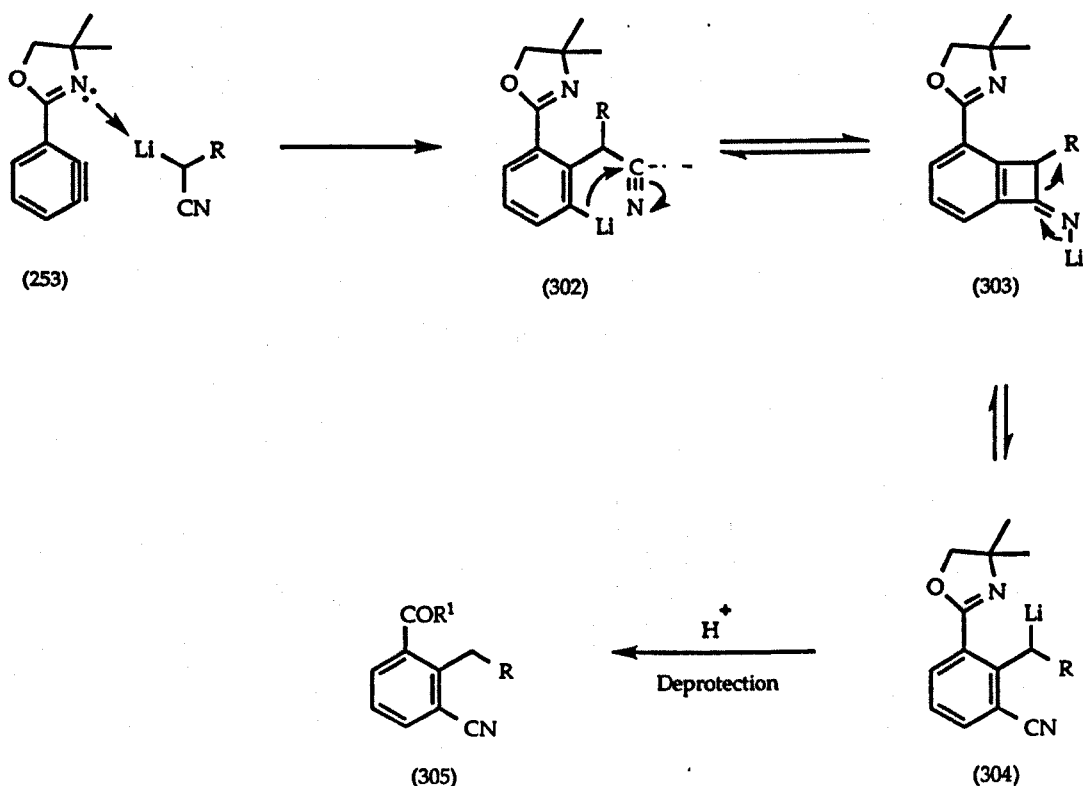
Scheme 102

The other general method of generating polycyclic ring systems *via* intermolecular trapping of benzyne concerns the introduction of a side chain nitrile group *via* the addition of aliphatic or aromatic nitrile anions *ortho* to substituted benzyne. This type of reaction has been applied to the synthesis of a number of synthetically useful 4-alkyl substituted derivatives of isochroman-3-one, which have been later utilised; for instance in the generation of *ortho*-quinodimethanes¹ and in the preparation of isoquinoline¹⁴⁰ and thioisoquinoline derivatives.¹⁴¹ Additionally, this route has been used by Biehl^{123c} to prepare 4-substituted isochroman-3-ones (301) *via* the addition of substituted nitriles to *ortho*-methoxymethyl-substituted benzyne (299), followed by subsequent ring closure and hydrolysis of the nitrile group (Scheme 103). This route was later used by the same author in the preparation of naturally occurring Protoberberins.



Scheme 103

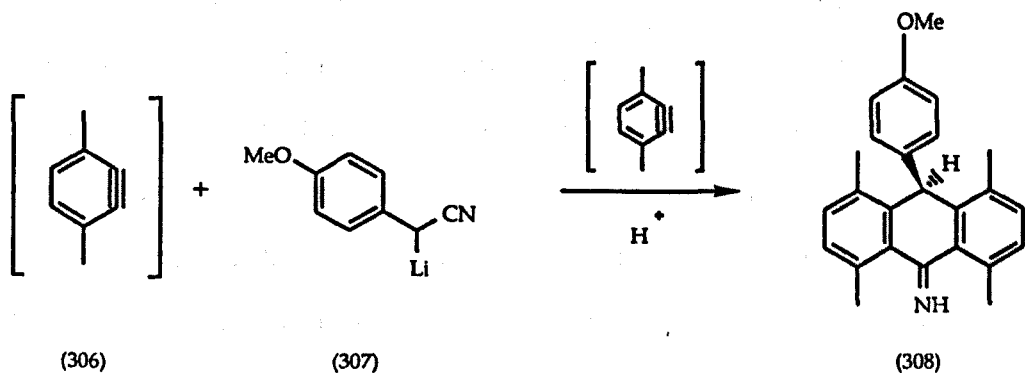
An interesting rearrangement of the product formed upon addition of lithiated nitrile species to benzyne has been observed by Meyers.¹⁴² When using aprotic solvents, the lifetime of the aryl anion in (302) is increased, therefore allowing it to attack the adjacent nitrile group to generate a benzocyclobutene (303). This unstable intermediate then undergoes rearrangement to yield a lithiated product (304), which is quenched *via* proton transfer to give the final product (305) (Scheme 104).



Scheme 104

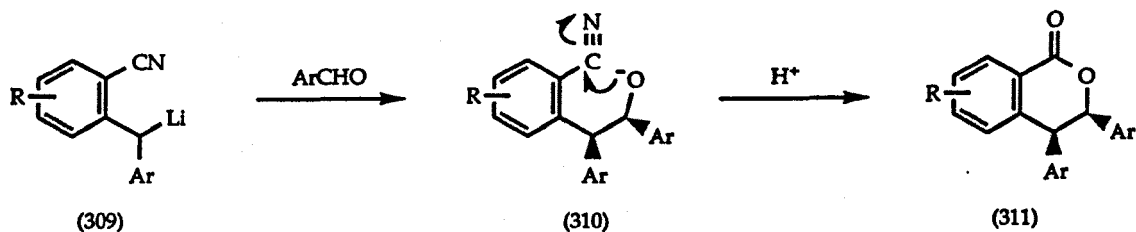
During the course of this tandem addition-rearrangement, two new groups are incorporated onto the aromatic ring, thus providing a useful route to either 1,2,3-trisubstituted aromatic aldehydes ($R^1 = H$) or carboxylic acids ($R^1 = OH$). The driving force for this reaction appears to be the extent to which substituents on the aromatic ring can either enhance the nucleophilicity of the aryl anion or stabilise the final lithiated product through complexation. Biehl^{123c} has suggested that benzyne precursors possessing at least two electron releasing substituents will undergo tandem addition-rearrangement reactions by increasing the nucleophilicity of the aryl anion, whereas precursors possessing fewer than two groups will yield simple benzyne adducts.

A similar tandem addition-rearrangement was encountered by Biehl when attempting isochroman-3-one formation upon switching from a protic solvent such as ammonia to an aprotic solvent such as THF (see *Scheme 103*).¹⁴³ This pathway has since been utilised by the same author in the synthesis of cyanophenothiazines (from simple phenothiazines)¹⁴⁴ and the synthesis of aminodipyridylisoquinoline derivatives *via* the addition of pyridylacetonitrile to suitably substituted benzyne.¹⁴⁵ One recently reported application of this synthetic route was the synthesis of a novel 9-imino derivative of anthracene (308) (*Scheme 105*).¹⁴⁶



Scheme 105

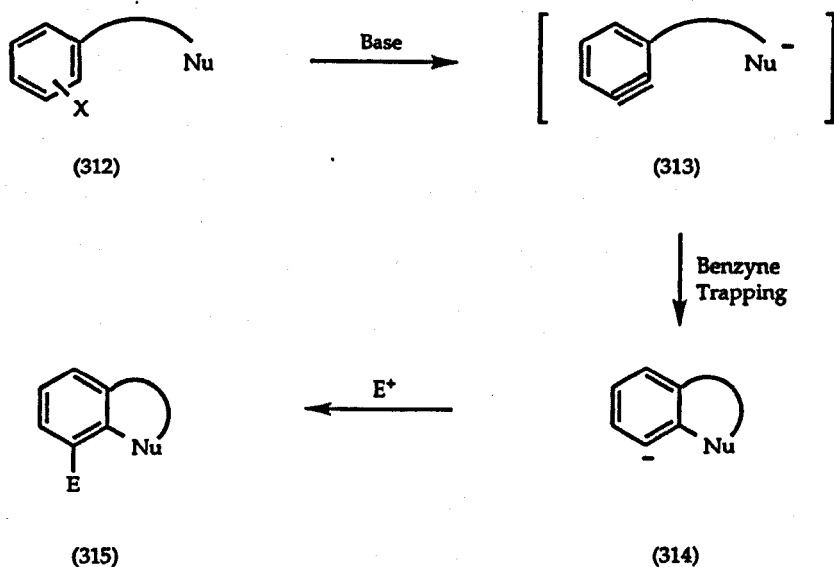
Biehl has also reported a variation on the tandem addition-rearrangement pathway, where intramolecular cyclisation in intermediate (310) resulting from nucleophilic attack by a flanking anion is followed by hydrolysis, to give cyclised products (Scheme 106). This route serves as a useful procedure for the synthesis of bicyclic species, and has been used for the synthesis of *cis*-3,4-diarylisochroman-1-ones (311).¹⁴⁷



Scheme 106

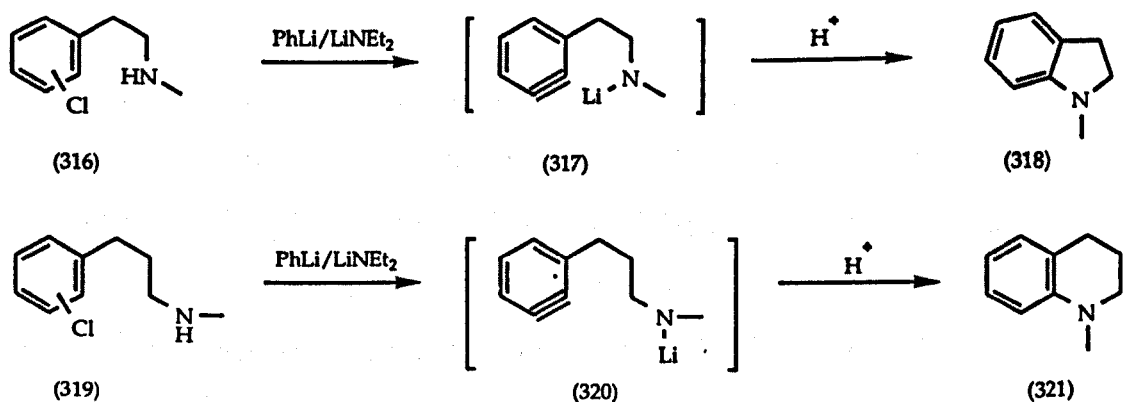
Intramolecular Nucleophilic Trapping of Benzyne

Another major application of benzyne in organic synthesis concerns their trapping in an intramolecular manner by flanking carbanionic or heteroatom nucleophiles positioned *ortho* or *meta* to the reactive intermediate, resulting in the generation of benzo-fused carbocycles or heterocycles (Scheme 107).^{36, 37, 123} Trapping of the generated aryl anion is achieved *via* either simple proton transfer (E = H), or the addition of external electrophiles (E = alkyl, acyl *etc.*). This procedure has been used to generate four, five and six membered rings (together with some examples of larger ring sizes), with the ability to use nucleophiles which otherwise show little affinity for the reactive triple bond. This has been attributed to favourable entropic factors, with the nucleophile held 'in place' for attack. Similar to intermolecular trappings, the choice of base and solvent is vital, as the nucleophile has to compete with the external base which is required for simultaneous benzyne generation and activation of the nucleophilic site.



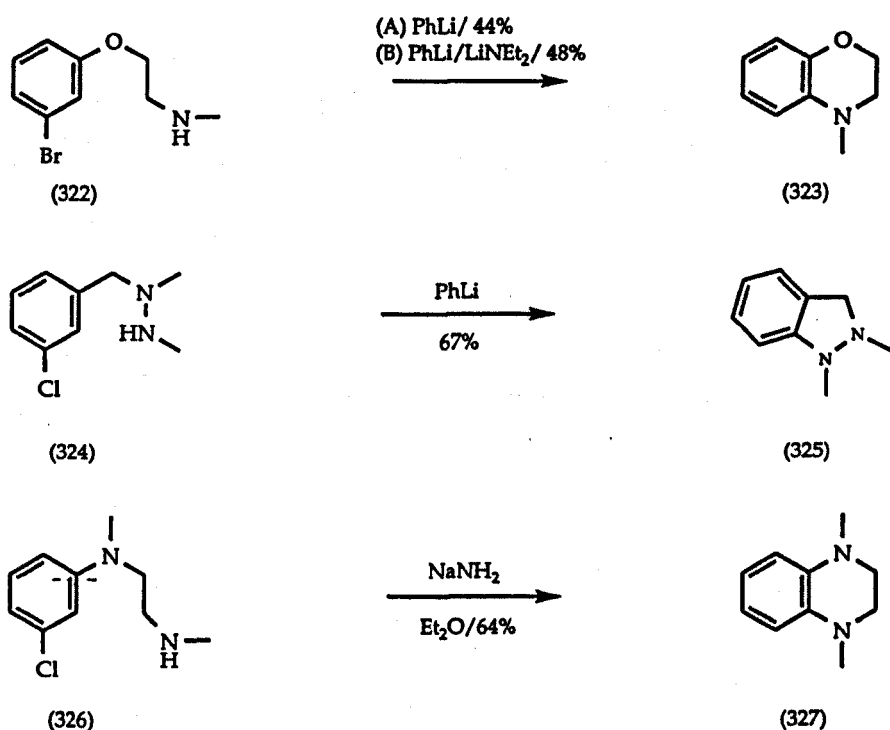
Scheme 107

Soon after the discovery of benzyne, Huisgen reported one of the first examples of intramolecular trappings of these reactive species, in the synthesis of benzo-fused nitrogen heterocycles *N*-methylindoline (318) and *N*-methyltetrahydroquinoline (321). Here, trapping of the benzyne (317) and (320) by secondary amines was accomplished upon treatment of the *ortho* or *meta*-substituted chlorobenzenes (316) and (319) with base (Scheme 108).^{78b} The same author later reported that the corresponding *N*-phenylquinolines could be prepared under similar conditions.



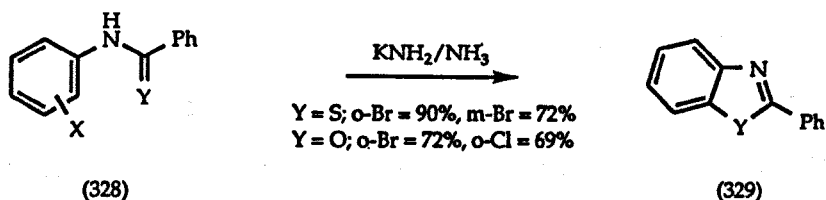
Scheme 108

In a similar manner to above, Huisgen reported the synthesis of other ring systems, including *N*-methylbenzomorpholines (323), *N,N'*-dimethylindazolines (325) and *N,N'*-dimethyltetraquinoxalines (327), all in moderate to good yields (Scheme 109).¹⁴⁸ The same author later reported the synthesis of larger ring systems containing eight, sixteen and seventeen atoms, again using secondary amines to trap benzynes, generated from *meta*-substituted aryl halides.⁶⁰



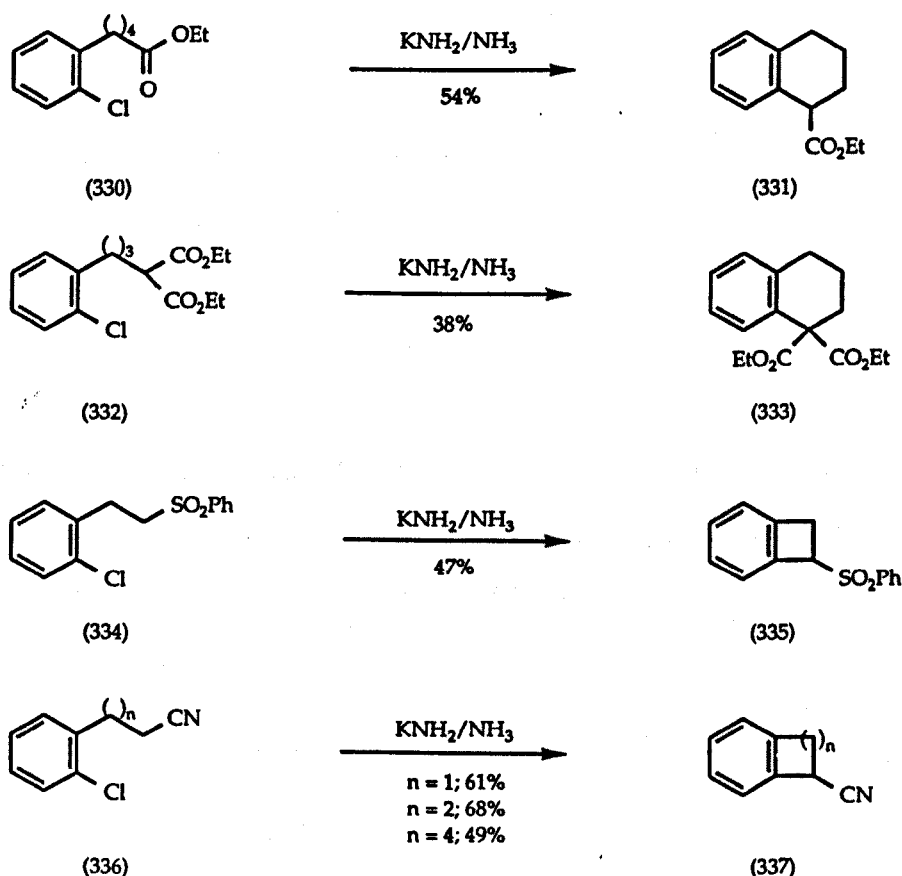
Scheme 109

Studies on the intramolecular trapping of benzynes using heteroatomic species other than nitrogen were undertaken by Bunnett.^{75, 76a} For example, the synthesis of 2-phenylbenzothiazole and 2-phenylbenzoxazole (329) was accomplished in good yields from the corresponding aryl bromides (328), with the process occurring *via* intramolecular nucleophilic attack by flanking sulphur and oxygen nucleophiles (Scheme 110).



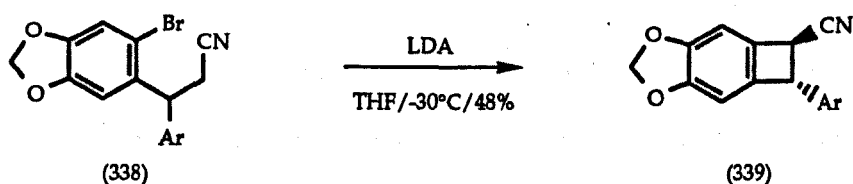
Scheme 110

In addition to the synthesis of benzo-fused heterocycles, the construction of bicyclic carbocycles *via* the trapping of benzyne by carbanionic nucleophiles was demonstrated by Harris and Hauser,¹⁴⁹ and also by Bunnett, who showed that carbanionic species derived from nitriles, ester enolates or metallated sulphones could take part in such reactions (Scheme 111).¹⁵⁰



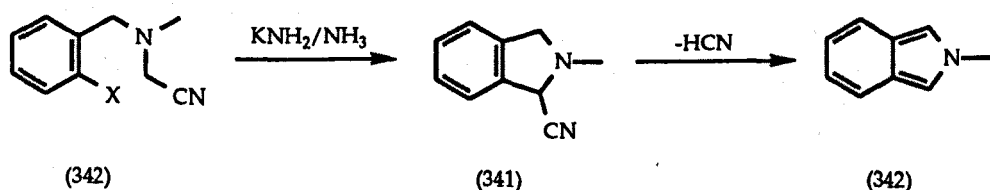
Scheme 111

The preparation of benzocyclobutenes (*e.g.* 337) *via* the intramolecular trapping of benzyne has been applied to many synthetic strategies, as this ring system provides a simple and effective route to *ortho*-quinodimethanes *via* electrocyclic opening upon thermolysis. One example is Oppolzers' preparation of the alkaloid Chelidonine (see Chapter One). The same author has also applied this route to the synthesis of terpene based compounds, as has the Kametani group.³⁶ Other natural product syntheses incorporating the formation of 1-cyanobenzocyclobutenes (339) have been reported, for example in the synthesis of Podophyllotoxin, an anti-tumour drug precursor (*Scheme 112*).⁶⁴ In their alternative synthesis of Podophyllotoxin, Durst and MacDonald generated a benzocyclobutene using a similar intramolecular trapping of benzyne, but by using an ester enolate species instead of a side chain nitrile.¹⁵¹



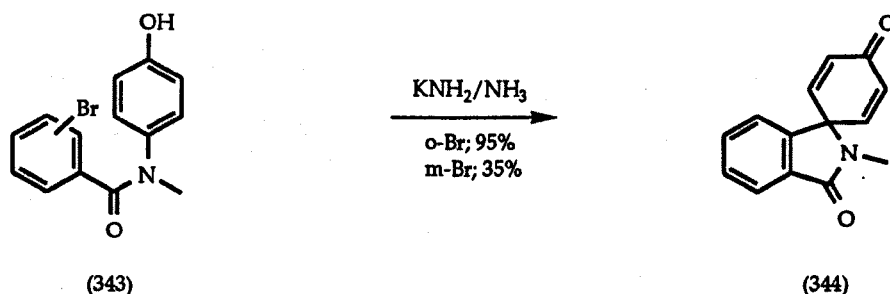
Scheme 112

Intramolecular trapping of benzyne by side chain nitriles has also been utilised in the synthesis of rings other than benzocyclobutenes; for example, in the synthesis of *N*-methylisoindole (342) (*Scheme 113*).¹⁵²



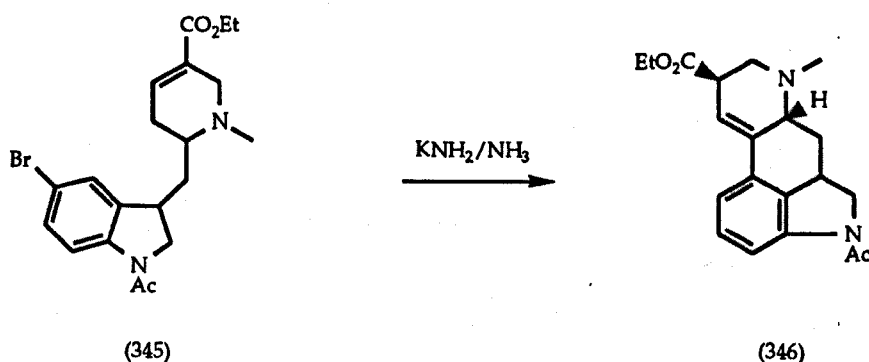
Scheme 113

In addition to the preparation of simple bicyclic intermediates, intramolecular trapping of benzyne has been applied to the formation of polycyclic ring systems. A classic example concerns the formation of a spiroannulated polycyclic species (344) from the aryl bromide (343) upon exposure to potassium amide, after conventional methods of synthesis had failed (Scheme 114).¹⁵³



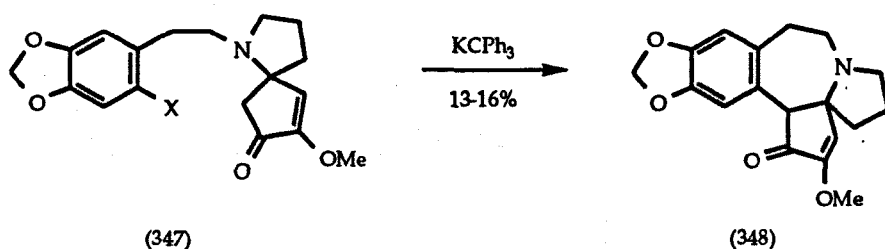
Scheme 114

Another classic example of polycyclic ring formation concerns the preparation of the polycyclic skeleton of Lysergic acid diethyl ester (346), in low yield, which was reported by Julia.¹⁵⁴ Here, the benzyne is generated from an aryl bromide (345), and is trapped by an anion formed *via* deprotonation of an α,β -unsaturated ester (Scheme 115). Low yields of product may have resulted from competing ring closure reactions involving the nitrogen atom in the six-membered ring.



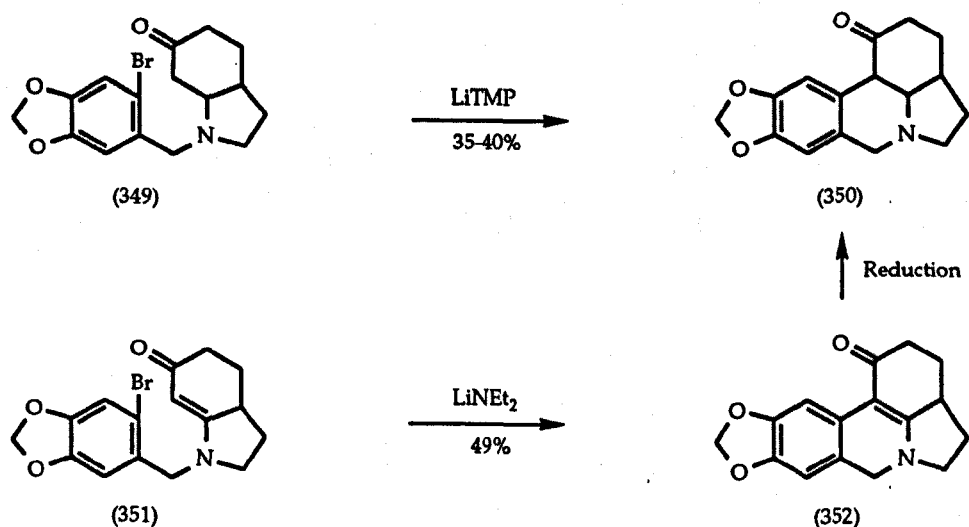
Scheme 115

Problems of competition between carbanions and other nucleophiles (resulting in low yields of the desired product) are also highlighted in Semmelhack's synthesis of Cephalotaxinone.¹⁵⁵ Formation of the tetracyclic skeleton (348), in low yield, was only achieved using potassium triphenylmethide as the base, with low yields resulting from a competing N-cyclisation process (Scheme 116).



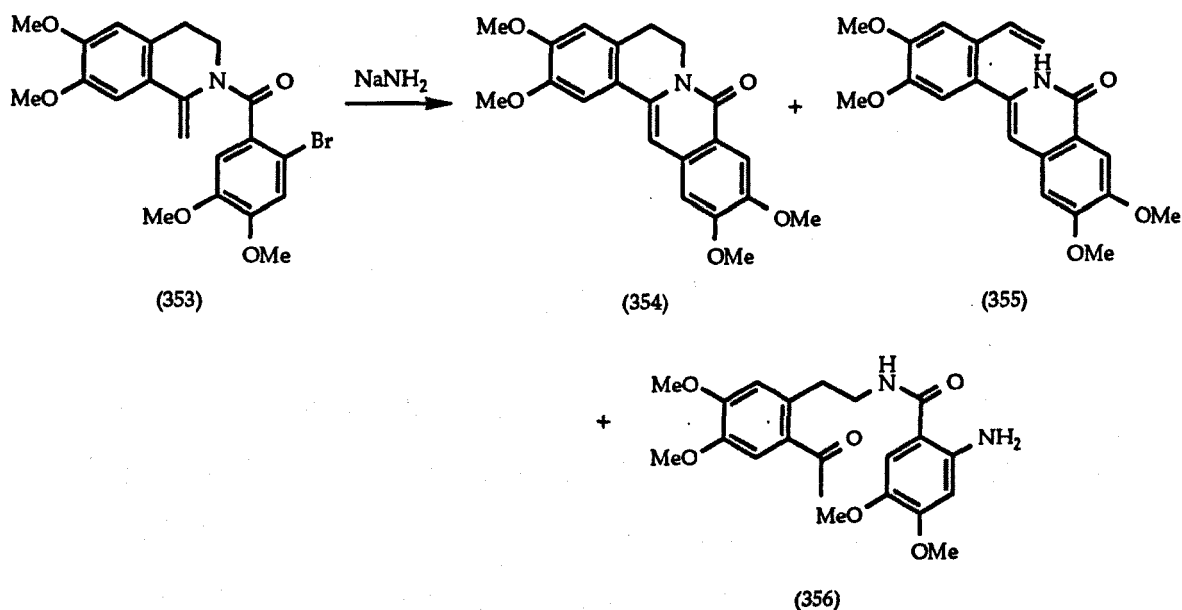
Scheme 116

The synthesis of the pentacyclic skeleton (350) of γ -Lycorane has been accomplished *via* the addition of an enolate species derived from the aryl bromide (349),¹⁵⁶ and also *via* the nucleophilic addition of a vinylogous amide onto a benzyne derived from an aryl bromide (351) (Scheme 117).¹⁵⁷



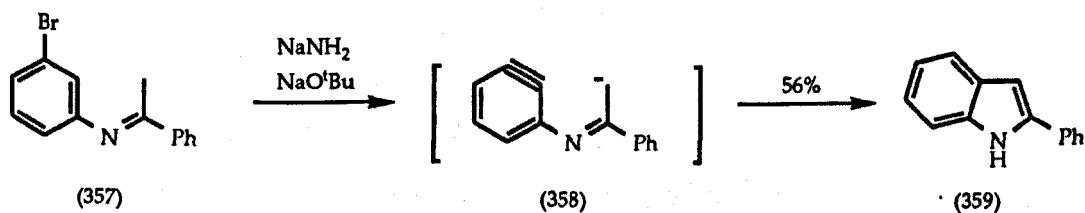
Scheme 117

Another nucleophilic centre which has been employed in intramolecular additions to benzyne is an enamide β -carbon, which Kametani has used in the synthesis of Xylopinene (Scheme 118).¹⁵⁸ Treatment of the aryl bromide (353) with sodium amide gives a mixture of isoquinolines (354) and (355), along with the amination-hydrolysis product (356). The cyclised material (354) was then isolated and reduced to give the natural product.



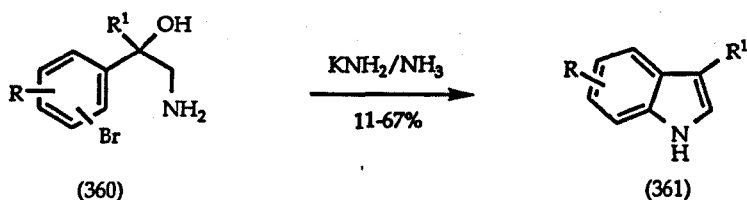
Scheme 118

Caubere *et al* have reported that terminal carbanionic species, derived from ketimines (357) by using a complex base system, can be used to trap benzyne in the synthesis of 2-substituted indoles (359) (Scheme 119).¹⁵⁹



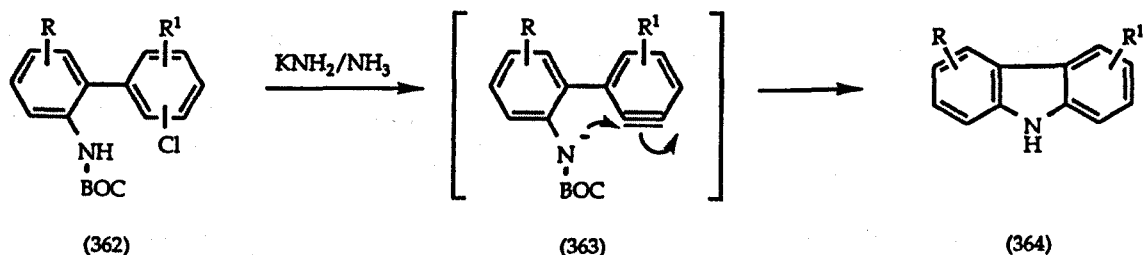
Scheme 119

Amine-derived anionic species have also been used to trap benzyne intermediates intramolecularly. Iida *et al*¹⁶⁰ have employed this route to the synthesis of dihydroindoles in an alternative synthesis of γ -Lycorane (*cf.* Scheme 117). Ahmed *et al*¹⁶¹ have reported the preparation of pyridinyl dihydroindoles *via* the trapping of 3,4-pyridynes, whilst Fleming has reported a similar route to 3-substituted indoles (361) *via* the action of potassium amide on bromoarylketones (360) (Scheme 120).¹⁶²



Scheme 120

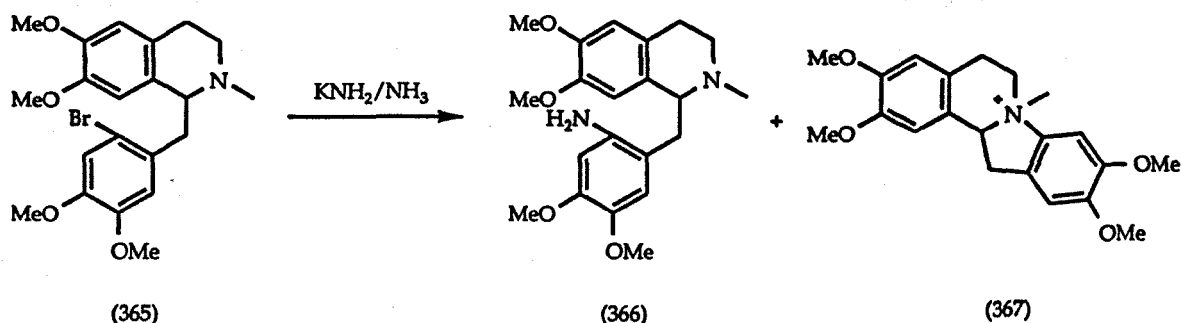
One recent example of the intramolecular trapping of benzyne by amine-derived anions was reported by Watanabe *et al*,¹⁶³ who showed that the synthesis of tricyclic ring carbazoles (364) could be achieved from aryl chlorides (362) in virtually quantitative yield (Scheme 121).



Scheme 121

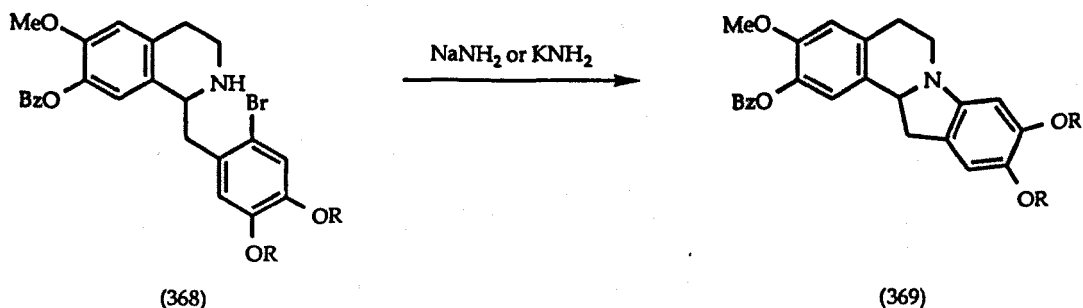
With the potential to create polycyclic ring systems in just one cyclisation step, the intramolecular trapping of benzyne by other aromatic ring systems holds obvious attractions. However, the prospects for achieving

such reactions appear to be low, as simple aromatic species tend not to be sufficiently nucleophilic. An example of this poor reactivity comes from the work of Ahmed and Gibson, where treatment of the aryl bromide (365) with potassium amide leads to only the amine (366) (35% yield), formed from amination of the generated benzyne, and the quaternary species (367), which is generated by attack by the tertiary amine (*Scheme 122*).¹⁶⁴



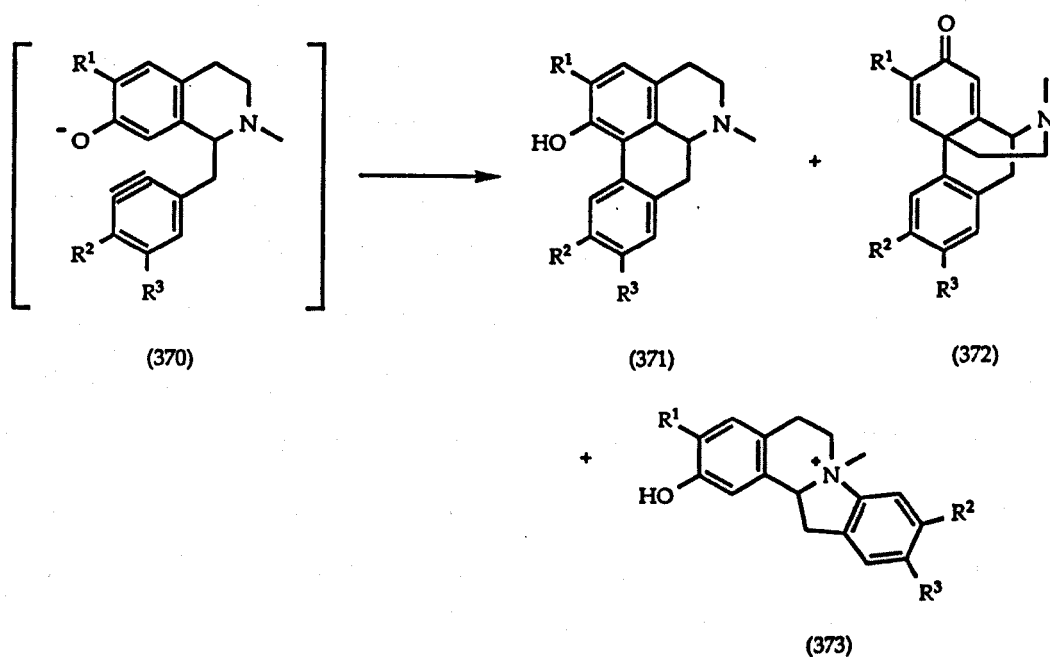
Scheme 122

As the quaternary salt (367) tends to undergo Hofmann degradation in basic media, the preparation of cyclic compounds such as these *via* attack of the nitrogen species has been accomplished using demethylated *N*-species, and the subsequent quaternisation of the isolated product. This has formed the basis of an efficient route to the formation of the ring skeleton (369) belonging to the dibenzindolizidine alkaloids Cryptausoline and Cryptowoline (*Scheme 123*).¹⁶⁵



Scheme 123

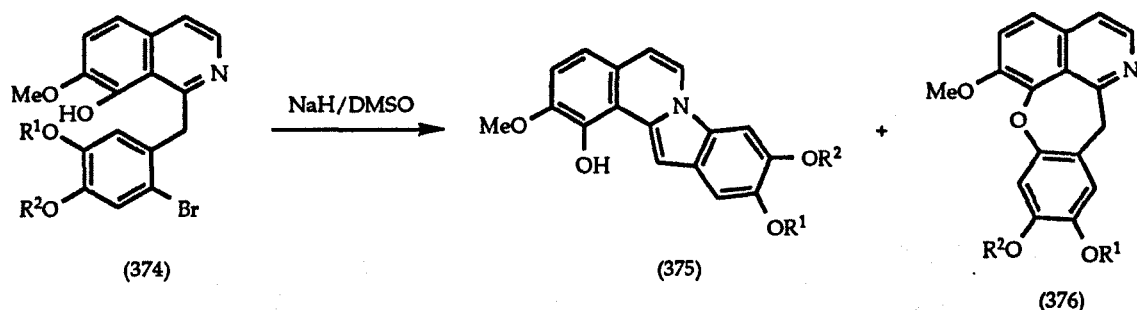
The potential for nucleophilic trapping by aromatic species can be improved by enhancing their reactivity; this can be achieved by the presence of an anionic group on the ring. For instance, the phenoxide anion in intermediate (370) activates the *ortho* site and allows the desired arylation leading to a synthesis of an Aporphine based skeleton (371). The phenoxide anion also activates the *para* site, giving rise to morphinandienones (372), and attack by the nitrogen nucleophile also takes place, resulting in dibenzindolizidine synthesis (373) (Scheme 124).¹⁶⁶ This type of activation by phenoxide anions has been utilised in the synthesis of many other related structures.



Scheme 124

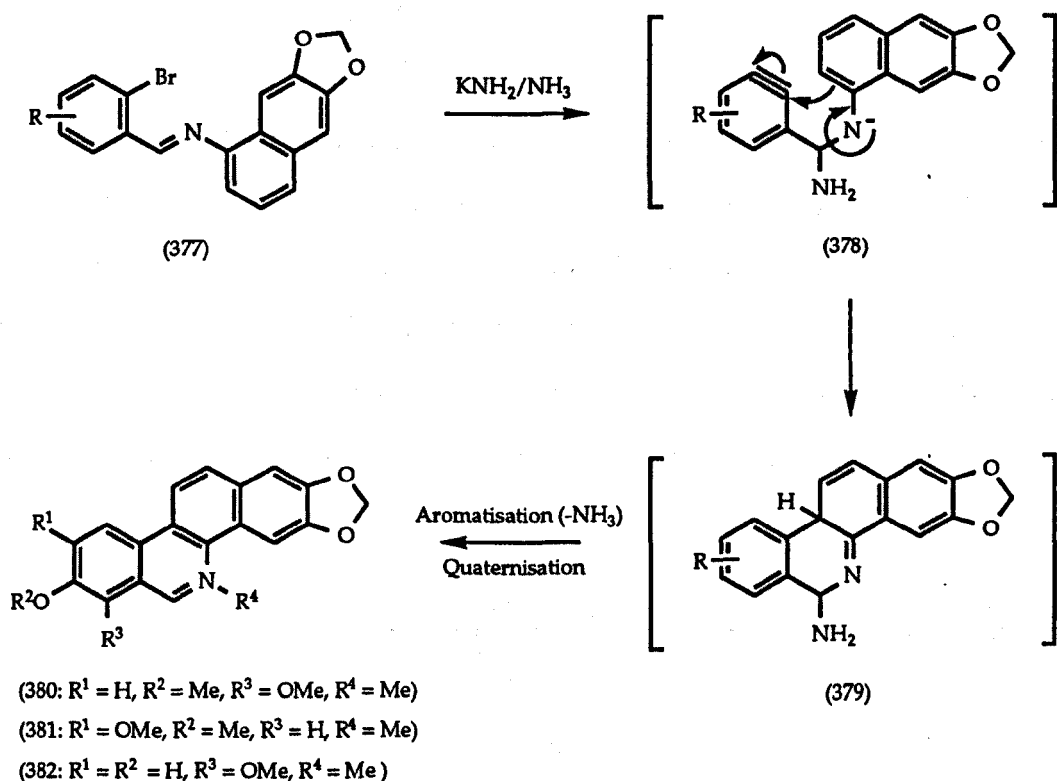
A similar approach to that outlined above was attempted by Castedo *et al* who reported the synthesis of the Cularine alkaloid skeleton (376) in low yields (20-25%) *via* the trapping of benzyne by the phenoxide anion. The poor yields appeared to be a result of favouring conditions for N-attack

(formation of a 5-membered ring), compared to 7-membered ring formation for *Q*-attack, and the higher nucleophilicity of the nitrogen species (Scheme 125).¹⁶⁷



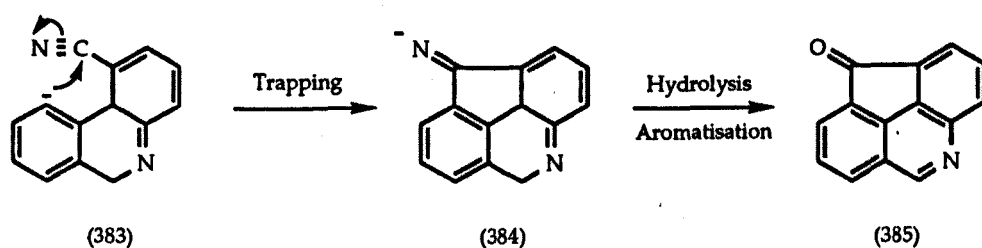
Scheme 125

Since nitrogen is more willing to share negative charge, amide-derived anions should act as better aryl activators than phenoxides, and this philosophy forms the basis of Kessars' extensive studies into the construction of polycyclic ring systems *via* the trapping of benzyne.^{63a} In the synthesis of naturally occurring benzo[*c*]phenanthridene alkaloids, Chelerythrine (380), Nitidine (381) and Decarine (382), cyclisation occurs even though the rings to be joined in the imine (377) are *trans*-disposed (Scheme 126). In addition to generating the benzyne in (378), amide ions add across the C=N bond and activate the aromatic ring, which is followed by cyclisation and the elimination of the amine group to yield the cyclised product (379). Higher yields of 8,9-oxygenated alkaloids such as Nitidine (381) (70% *vs.* 10%) were obtained using LDA rather than potassium amide to generate the benzyne. Kessar has applied this route to the synthesis of phenanthridene and dihydrophenanthridene both in excellent yields, and to the one-step synthesis of pentacyclic compounds *via* a double benzyne cyclisation.^{123b} Recently, this methodology was applied to the synthesis of benzo-[*c*][2,7]-naphthyridenes.¹⁶⁸



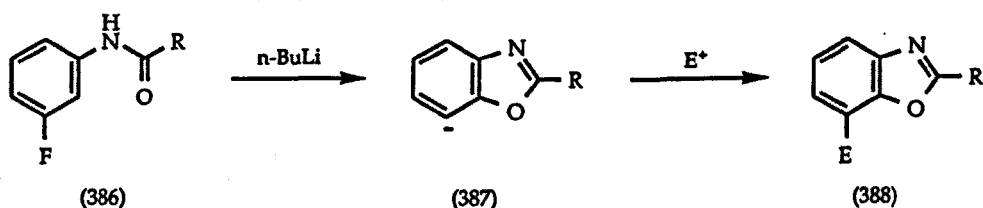
Scheme 126

The trapping of aryl anions, generated from the intramolecular trapping of benzyne, by electrophiles has also been applied in organic synthesis. Kessar¹⁶⁹ first reported an example of such a process when attempting phenanthridene synthesis, where isolation of the expected cyanophenanthridene was accompanied by the formation of a tetracyclic ketone (385), obtained by the intramolecular trapping of an adjacent nitrile group by the aryl anion in intermediate (383) (Scheme 127).



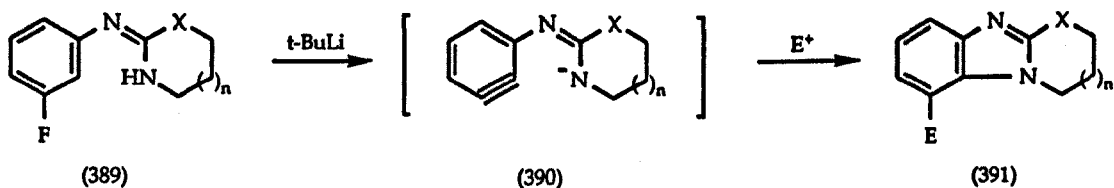
Scheme 127

Repeating Bunnett's early studies on the synthesis of 2-phenylbenzoxazole (see *Scheme 110*), Clark and Caroon demonstrated the ability to trap the generated aryl anion in (387) resulting from benzoxazole synthesis with a range of external electrophiles, leading to the synthesis of 2,6-disubstituted benzoxazoles (388) (*Scheme 128*).¹⁷⁰ A similar approach has also been used in the synthesis of 1,2,3,4-tetrasubstituted benzenes.¹⁷¹ Additionally, the synthesis of polysubstituted aromatic acids *via* trapping of an aryl anion with carbon dioxide has also been reported.¹⁷²



Scheme 128

In a similar fashion, Caroon and Fisher reported the preparation of tricyclic 1,2-annulated benzimidazoles (391) *via* intramolecular benzyne trapping by neighbouring amide derived anions, and quenching of the aryl anion with external electrophiles (*Scheme 129*).¹⁷³



Scheme 129

CHAPTER FOUR

Cycloaddition Reactions of Benzyne

- a) *Introduction*
- b) *Cycloaddition to 1,3-Dienes: Diels-Alder Reactions*
- c) *[2 + 2] Cycloadditions of Benzyne*
- d) *[1,3]-Dipolar Cycloadditions of Benzyne*
- e) *Summary*

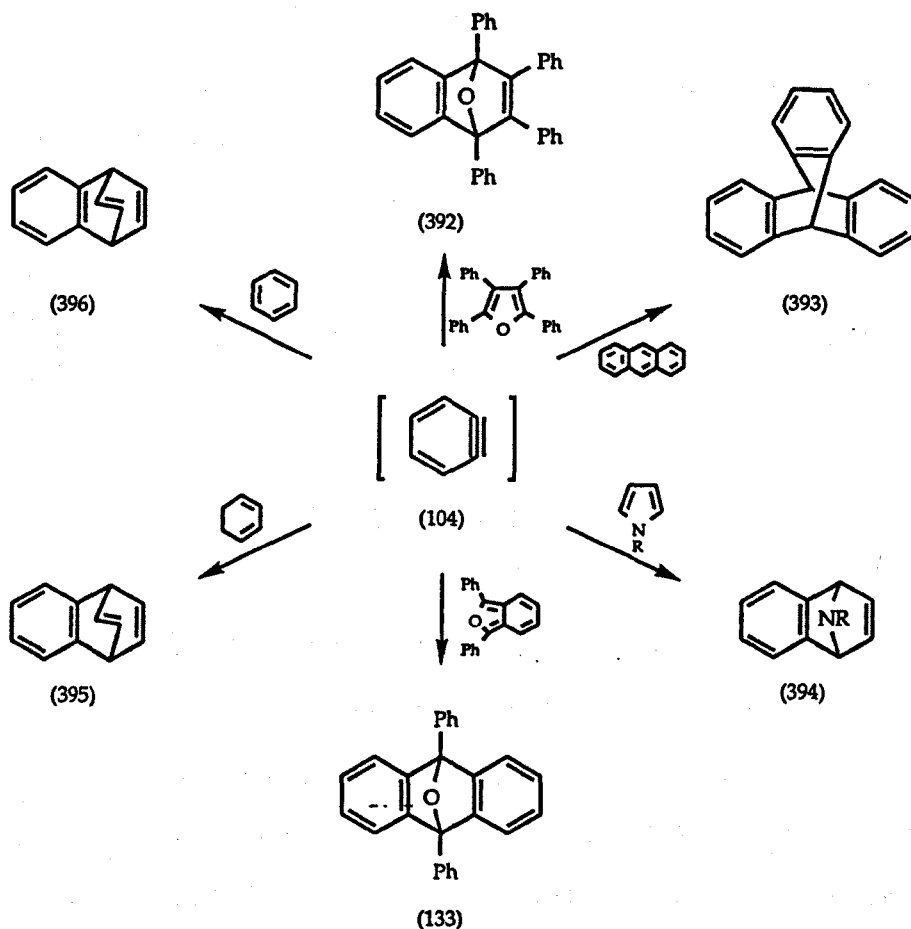
a) Introduction

In addition to the high electrophilicity that benzyne possess, the unstable 'acetylenic' nature of the arynic triple bond also enables these species to take part in various pericyclic processes.^{36, 37} Unfortunately, as for nucleophilic reactions of benzyne (see Chapter Three), problems concerning the construction of suitably substituted benzyne precursors, the use of nucleophile-derived reagents for benzyne generation and the side reactions that benzyne will take part in, all contribute to a relative lack of exploitation of pericyclic reactions of benzyne in organic synthesis.

b) Cycloaddition to 1,3-Dienes: Diels-Alder Reactions

Since Wittig's discovery that benzyne behave as highly reactive dienophiles in cycloaddition reactions with furan (see *Scheme 32*),⁴² the ability of benzyne to take part in Diels-Alder reactions with 1,3-dienes, in particular with heterocyclic species, where the *cis* nature of the diene is fixed and activated, has been regarded as one of their most distinguishing features.^{36, 37} Because the reaction between *ortho*-benzyne (104) and furan is so high yielding, it has become established as a diagnostic test for the formation of benzyne from newly developed precursors. Similarly, the high yielding reactions with dienes such as tetraphenylfuran leading to the formation of compound (392), anthracene leading to the formation of triptycene (393), pyrroles leading to the formation of compound (394), and 1,3-diphenylisobenzofuran leading to the formation of compound (133) have also become diagnostic tests. Further indications of the affinity of *ortho*-benzyne for Diels-Alder reactions has also been highlighted by its' ability to take part in reactions with relatively unreactive 1,3-dienes, such as

cyclohexadiene, leading to the formation of compound (395), and even with highly stable diene containing species such as benzene, leading to the formation of compound (396) (Scheme 130).^{36, 37}

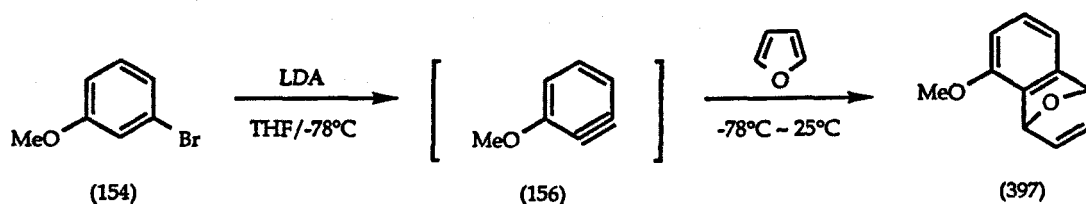


Scheme 130

Intermolecular Diels-Alder Reactions in Organic Synthesis^{123, 174}

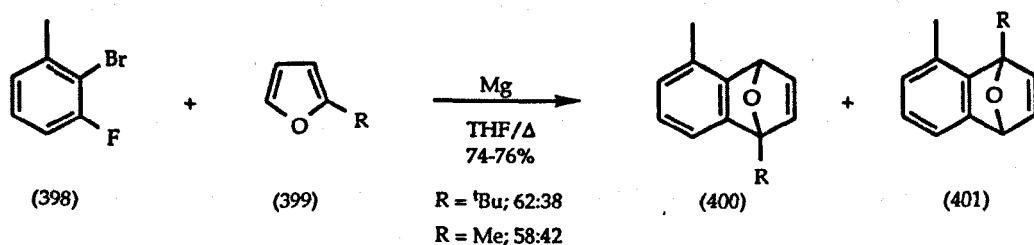
Of the cyclic 1,3-dienes that have been utilised in Diels-Alder cycloadditions in organic synthesis, the high affinity of furan for benzyne has received much attention. However, the application of this reaction in organic synthesis has only started to surface in recent years, with the onset of non-nucleophilic, hindered basic reagents which minimalise interaction

between reagents and benzyne, thus allowing the reactive intermediate to take part in desired reactions. For example, in their studies on the use of LDA for benzyne generation from aryl bromides (see *Scheme 42*), Jung and Lowen demonstrated that Diels-Alder cycloadditions between substituted benzyne and furan could be achieved in respectable yields. Additionally, 3-methoxybenzyne (156) also underwent cycloaddition with furan in similar yields (~ 50%) (*Scheme 131*).⁶⁴



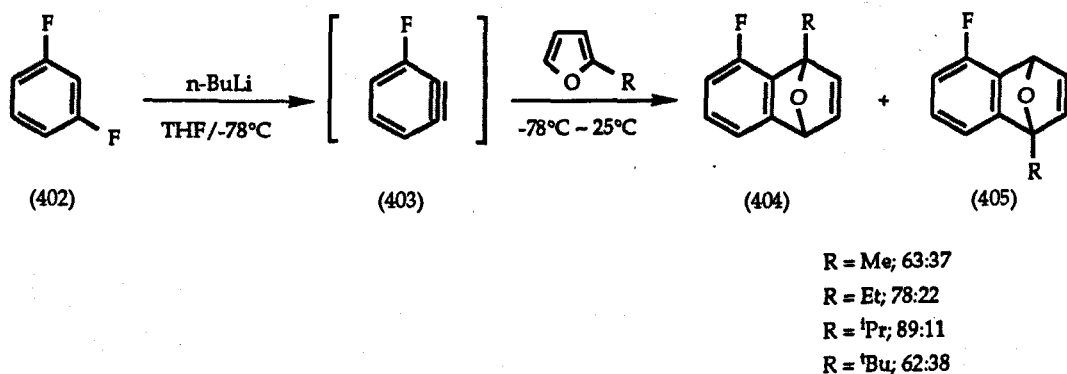
Scheme 131

An additional problem concerning Diels-Alder reactions of benzyne arises when intermolecular reactions between unsymmetrical benzyne and unsymmetrical 1,3-dienes are attempted, as problems of regioselectivity in the resulting cycloadduct arise. One example which highlights this problem is the cycloaddition of 2-substituted furans (399) to 3-methylbenzyne, where two possible regioisomers (400) and (401) are formed in comparable proportions regardless of the substituent size and the method used to generate the benzyne (*Scheme 132*).¹⁷⁵



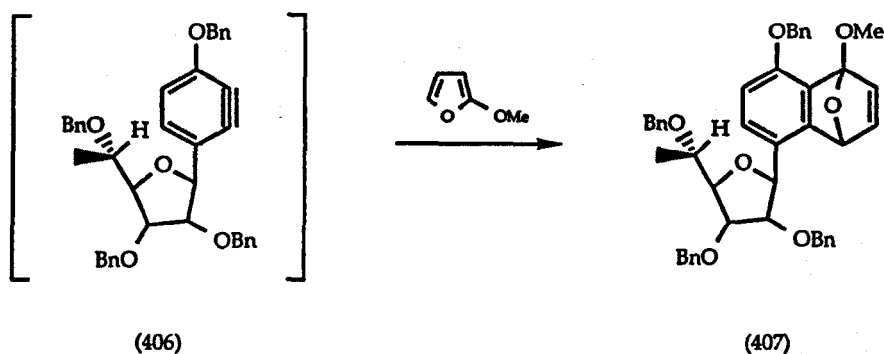
Scheme 132

Although Diels-Alder reactions between unsymmetrical benzyne and unsymmetrical 1,3-dienes remain on the whole to be rather unselective, several examples of unanticipated regioselectivity have been reported.¹⁷⁶ One example was reported by Gribble *et al*,¹⁷⁷ who demonstrated that Diels-Alder cycloadditions between 3-fluorobenzyne (403) and 2-alkylfurans can be achieved with a certain degree of regioselectivity, increasing in favour of the *syn* adduct in the order $R = \text{Me} < \text{Et} < \text{t-Bu}$, and through to roughly 9:1 ratios for the larger isopropyl substituent (Scheme 133). Regioselectivity in the cycloaddition was rationalised by a steric effect between the substituents in the benzyne and furan rings, in the concerted non-synchronous transition state.



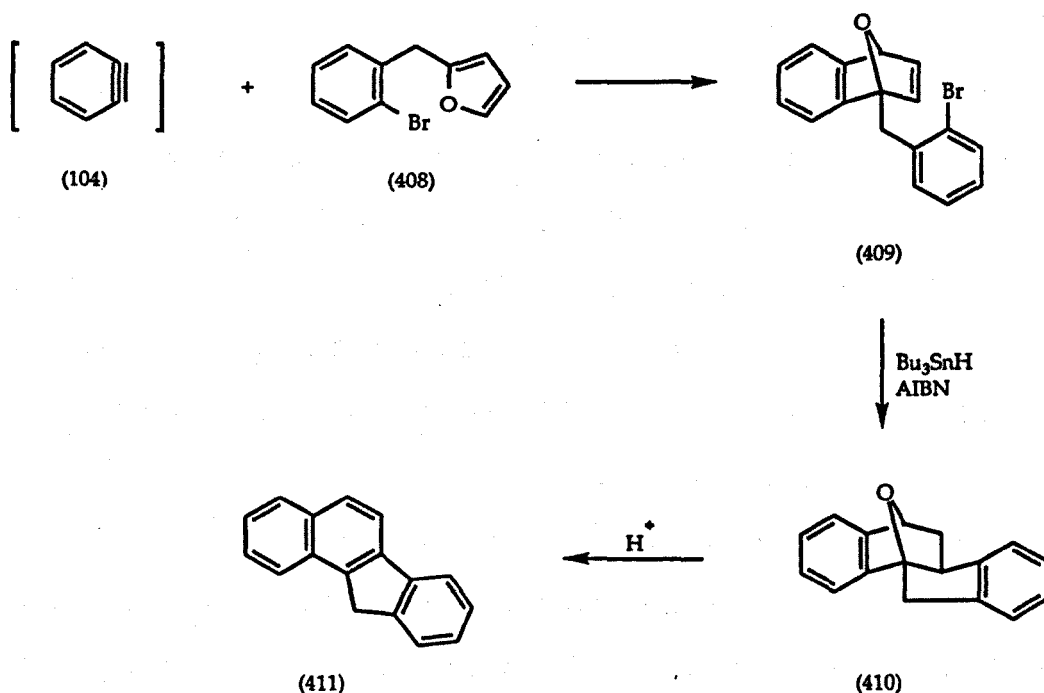
Scheme 133

A similar regioselective reaction between an unsymmetrical benzyne and an unsymmetrical furan was recently reported during the total synthesis of the C-glycoside antibiotic Gilvocarcin M (Scheme 134).¹⁷⁸ The observed regioselectivity of the addition of 2-methoxyfuran to a 3-benzyloxy-substituted benzyne (406) (9:1 in favour of the *syn* adduct) was attributed by the authors as a consequence of the polarisation of the reactive triple bond by the benzyloxy substituent in the benzyne.



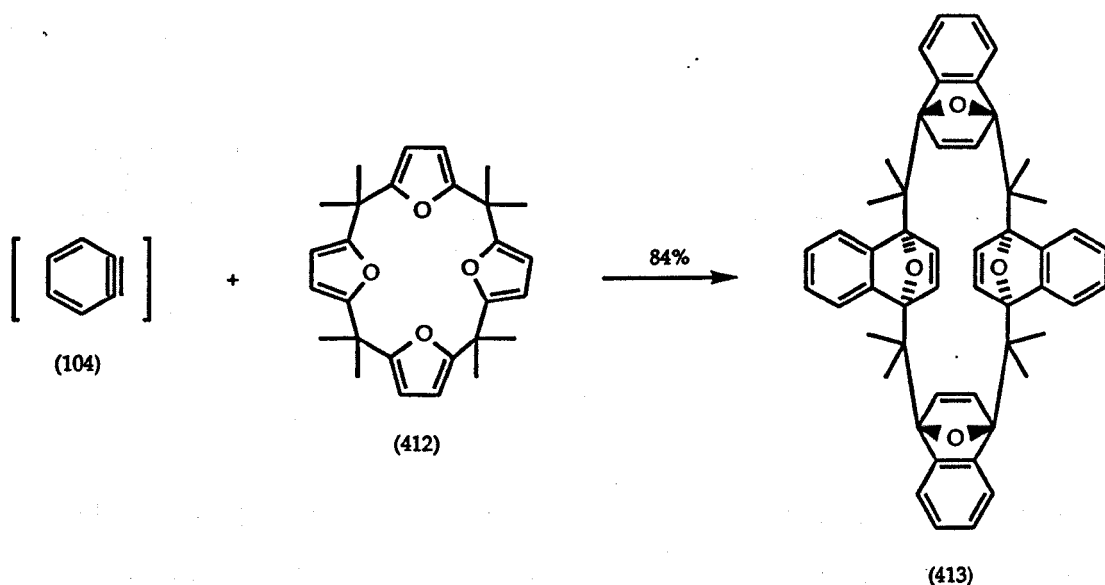
Scheme 134

Diels-Alder reactions of benzyne have been extensively covered by Hart and co-workers.¹⁷⁹⁻¹⁸¹ For example, a tandem cycloaddition-radical cyclisation process leading to the rapid assembly of polycyclic systems (*e.g.* 411) has been reported, whereby an initial Diels-Alder reaction between benzyne and a furan containing a suitably placed aryl or vinyl bromide is followed by a radical cyclisation/aromatisation sequence (Scheme 135).¹⁷⁹



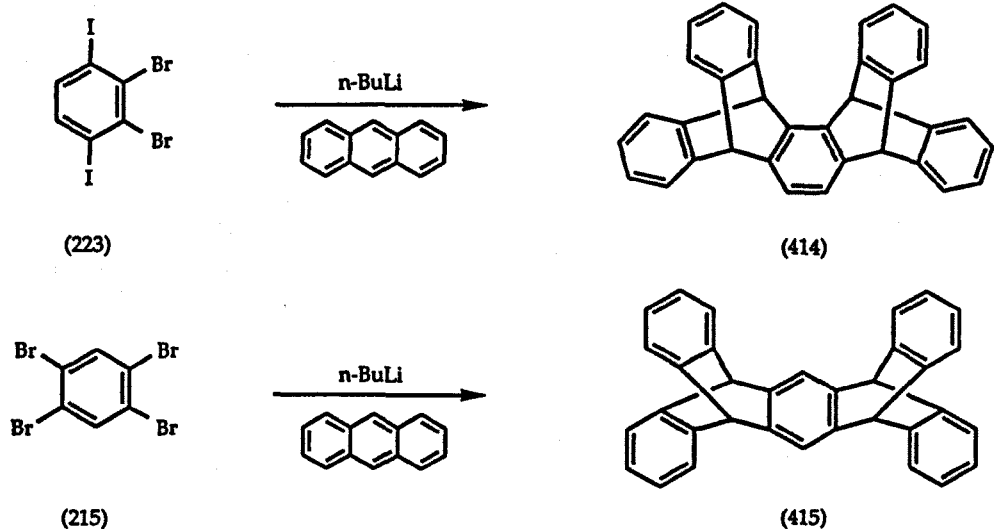
Scheme 135

Hart has also reported a one-step, fourfold and extremely efficient cycloaddition of *ortho*-benzyne (104) to a tetrafuran macrocycle (412), leading to the synthesis of the macrocyclic species (413) (Scheme 136).¹⁸⁰



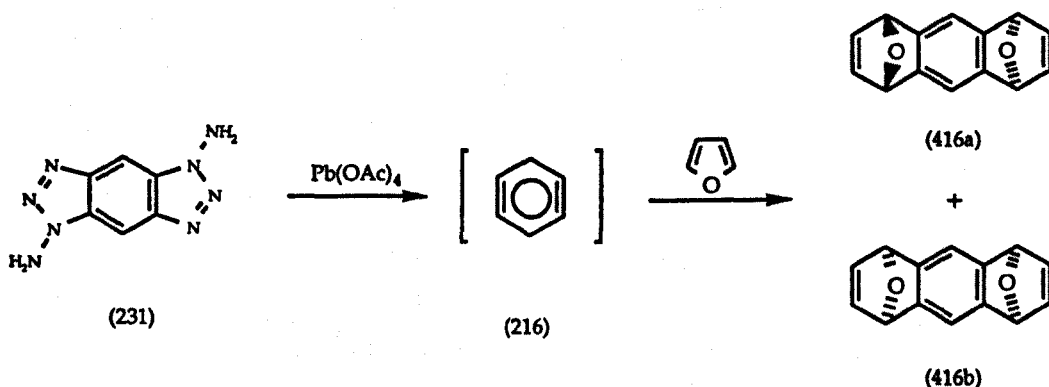
Scheme 136

bis-Aryne equivalents have also been utilised by Hart and co-workers in Diels-Alder chemistry, where *bis*-annulation between these reactive species and certain 1,3-dienes serves as a very useful and rapid route to polycyclic ring systems. Hart has described the elegant syntheses of a range of angular iptycenes (e.g. 414 and 415) by applying the efficient reaction between *ortho*-benzyne, generated from polyhalogenated aromatic species, and anthracene, to his own studies (Scheme 137).¹⁸¹ It has been proposed that the *bis*-annulation probably occurs in a sequential, stepwise manner.^{114, 117} The same author has also conducted extensive studies into the *bis*-annulations between *bis*-arynes and a range of furans and pyrroles, thus providing a useful route to substituted anthracenes and phenanthrenes, following removal of the oxygen and sulphur bridges in the initial cycloadducts.¹¹²



Scheme 137

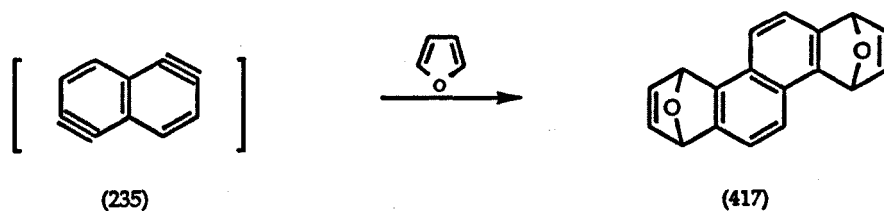
Hart has also reported the use of the *bis*-aminobenzotriazole (231) in *bis*-annulations. In the addition of furan to 1,4-benzdiyne (216), a significant ratio of *anti*: *syn* products was isolated in favour of the *anti* product (416a: 416b) (77:23),¹¹⁶ compared to the use of 1,2,4,5-tetrabromobenzene, where the ratio was roughly equal (55:45) (Scheme 138).¹¹²



Scheme 138

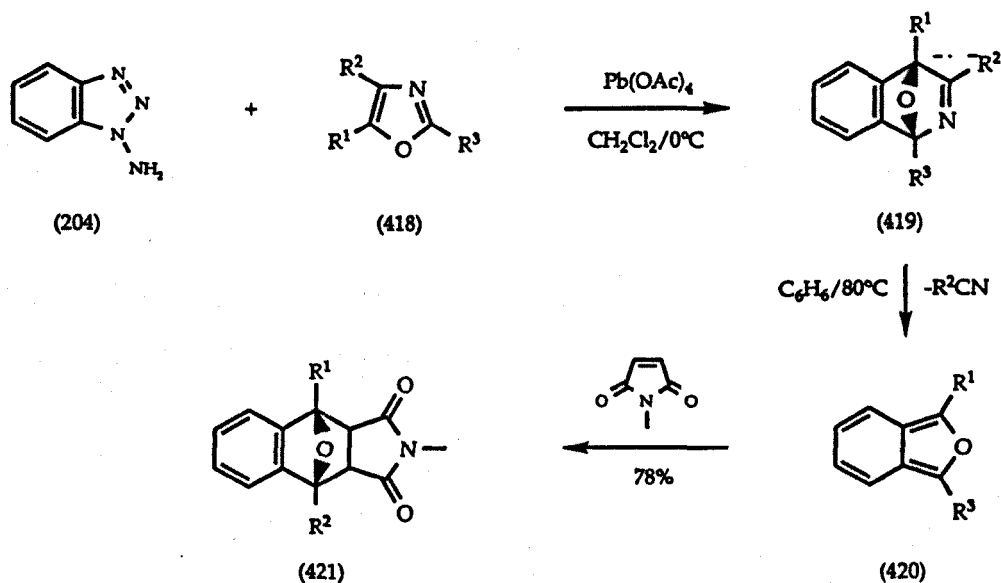
An analogous route to polycyclic products using *bis*-aryne equivalents was reported by Gribble *et al*, who reported that the synthesis of the

polycyclic skeleton (417) of Chrysene could be effected by the *bis*-annulation of a 1,5-naphthodiyne equivalent (235) with furan (Scheme 139).¹¹⁸



Scheme 139

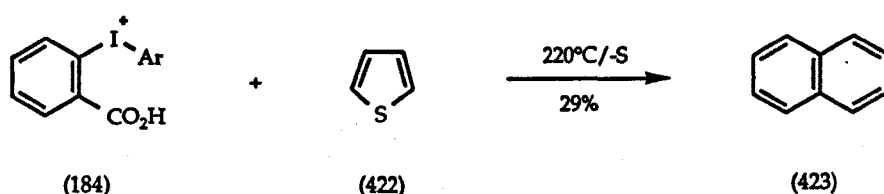
Diels-Alder cycloadditions between benzyne and other heteroaromatic 1,3-dienes have also been reported, although mainly with oxazoles, and generally not with other heteroaromatic species.¹⁸² One recent example concerned the cycloaddition of *ortho*-benzyne with substituted oxazoles (418),¹⁸³ with *retro*-Diels-Alder rearrangement of the cycloadduct (419) leading to isobenzofuran synthesis (420) (Scheme 140).



Scheme 140

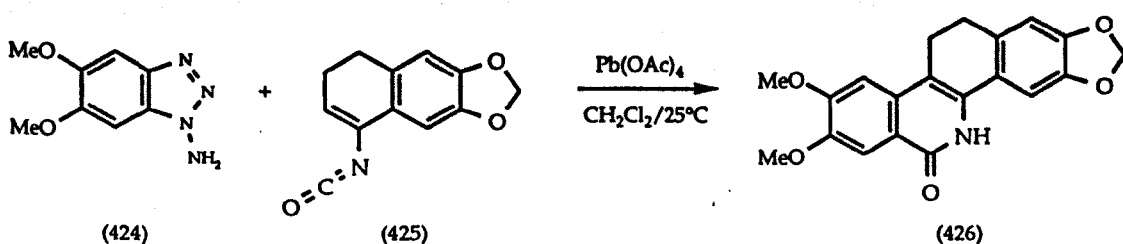
The potential for thiophene (422) to take part in Diels-Alder reactions

with benzyne was comprehensively studied by Del Mazza and Reinecke using six different benzyne precursors.^{87c} In doing so, they demonstrated that this heterocycle exhibited poor dienic reactivity towards *ortho*-benzyne, compared to other heteroatoms such as furans and pyrroles, with top yields of 29% for the Diels-Alder cycloadduct (423) being obtained under the forcing conditions required when using diphenyliodonium-2-carboxylate (184) (Scheme 141).



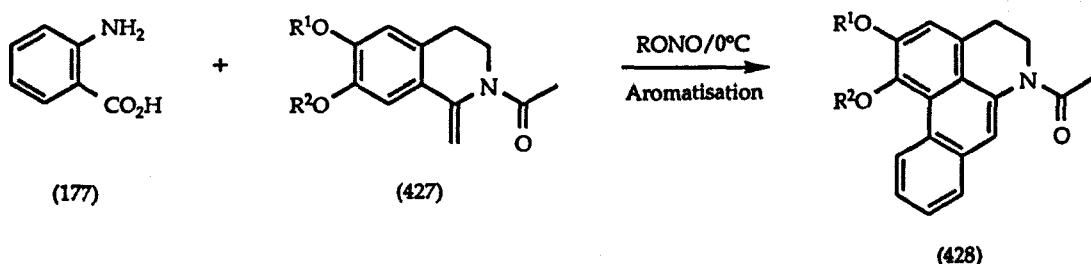
Scheme 141

The 1-aminobenzotriazole route to benzyne has also been used by Rigby *et al*,¹⁸⁴ who demonstrated that *ortho*-benzyne takes part in cycloadditions with a range of vinyl isocyanates leading to phenanthridenes and benzo[*c*]phenanthridenes. This route was recently applied by the same authors to the total synthesis of the benzo[*c*]phenanthridene alkaloid *N*-Nortidine, where construction of the skeleton (426) was achieved using the substituted 1-aminobenzotriazole (424) in conjunction with the vinyl isocyanate (425) (Scheme 142).¹⁸⁵



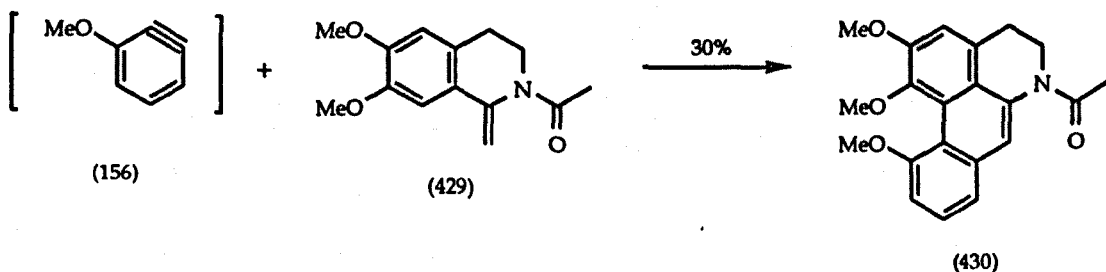
Scheme 142

Extensive studies into the use of intermolecular Diels-Alder reactions of benzyne for natural product synthesis have been conducted by Castedo and his co-workers.¹⁸⁶ For the construction of phenanthrene alkaloids, styrenes have been used as the diene components, with the diene conformation being fixed, thus eliminating problems concerning regioselectivity. For example, alkylidenetetrahydroisoquinolines (427; $R^1 = R^2 = \text{alkyl}$) have been trapped with *ortho*-benzyne to give a cycloadduct (428), which is converted into Aporphines and Noraporphines (Scheme 143).



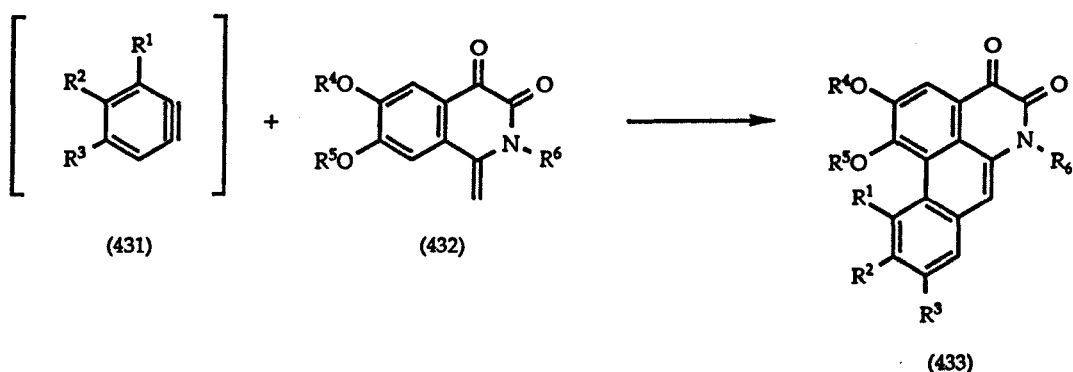
Scheme 143

Cycloadditions between alkylidenetetrahydroisoquinolines (429) and unsymmetrical *ortho*-methoxysubstituted benzyne (156) have been found to be totally regioselective, and this has been used in the preparation of substituted Aporphinoids (430), which are otherwise difficult to obtain (Scheme 144).¹⁸⁶



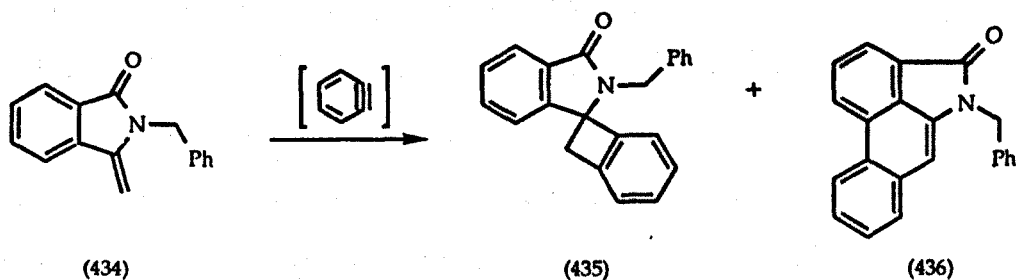
Scheme 144

This approach to Aporphines was applied by Castedo to the synthesis of a whole range of Aporphinoid-based species, and Apomorphine analogues.¹⁸⁷ Amongst the groups of Aporphinoids synthesized were Dehydroaporphines and naturally occurring 4,5-Dioxoaporphines (433) using substituted benzyne (431) and methylene isoquinoline derivatives (432) (Scheme 145).¹⁸⁶



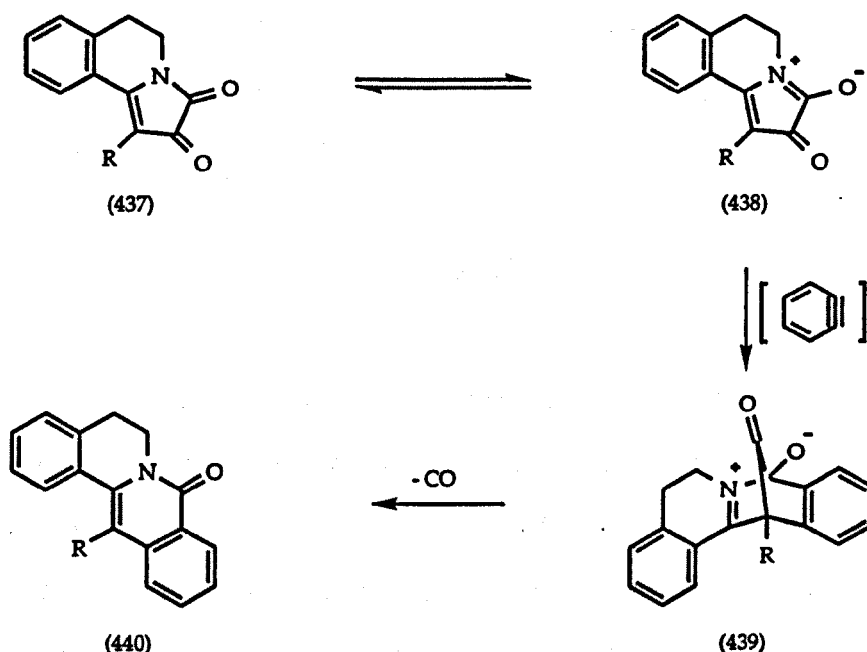
Scheme 145

The synthesis of Aristolactams (*e.g.* 436) has also been reported by Castedo, when attempting Diels-Alder cycloaddition between methylenaphthalimines (434) and benzyne (Scheme 146).¹⁸⁶ The isolation of the benzocyclobutene appeared to be favoured due to the greater distance between the termini of the diene, decreasing the potential of the intended Diels-Alder reaction.



Scheme 146

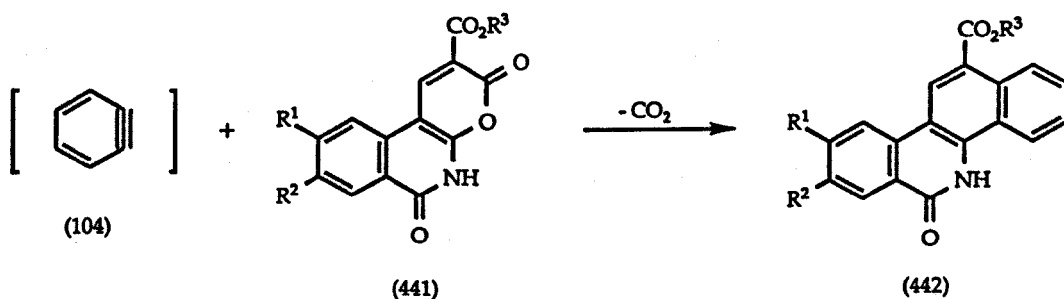
Castedo has also reported another approach to naturally occurring alkaloids *via* an intermolecular Diels-Alder process, where cycloaddition between various substituted isoquinoline pyrroline-2,3-dione species (437) and benzyne is followed by extrusion of carbon monoxide, leading to 3-isoquinolones (440) (Scheme 147).¹⁸⁸



Scheme 147

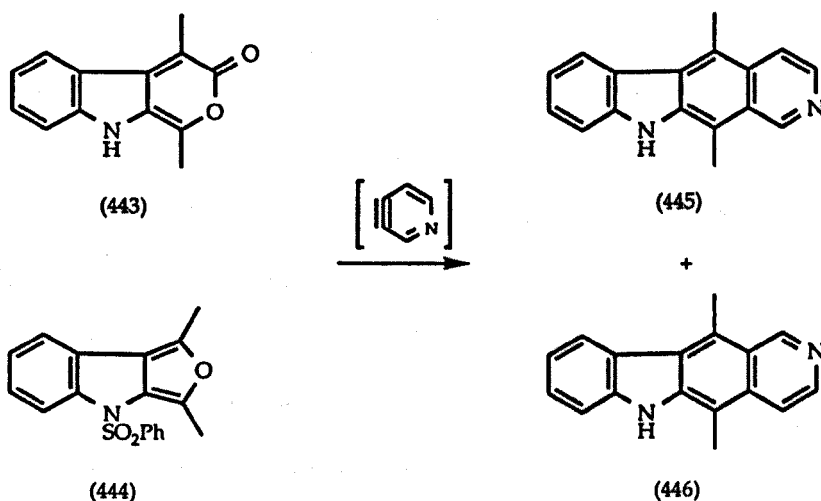
Due to the presence of two electron-withdrawing carbonyl groups in the pyrroline-2,3-dione ring system, the proton ($R = H$) positioned adjacent to these two carbonyl groups is highly acidic and, under the basic conditions required to generate the benzyne, this site will be activated and will interfere with the desired cycloaddition by trapping benzyne *via* nucleophilic addition. A substituent ($R = \text{alkyl}$) therefore has to be included to prevent activation. This approach has been utilised in the synthesis of Protoberberines, Dehydroyohimbanes, and the benzo[*c*]phenanthridene alkaloids Nitidine and Chelerythrine (*cf.* Scheme 126).

An alternative route to benzo[*c*]phenanthridene alkaloids has been reported by Castedo *et al*,¹⁸⁹ where construction of the skeleton (442) is achieved *via* the cycloaddition between *ortho*-benzyne (104) and a 1,3-diene in the form of a pyrone (441) (Scheme 148).



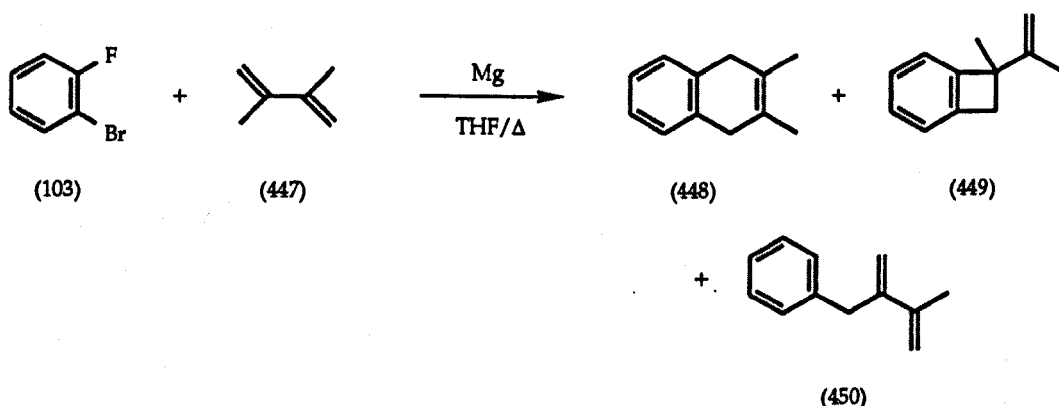
Scheme 148

May and Moody attempted a Diels-Alder reaction between a pyrone (443) and 3,4-pyridyne, in their synthesis of the anti-tumour agent Ellipticene (445).^{86c} A 1:1 mixture of this compound and its isomeric form Isoellipticene (446) was obtained. Gribble *et al*¹⁹⁰ obtained a similar result by trapping the same pyridyne with a suitable isobenzofuran (444).



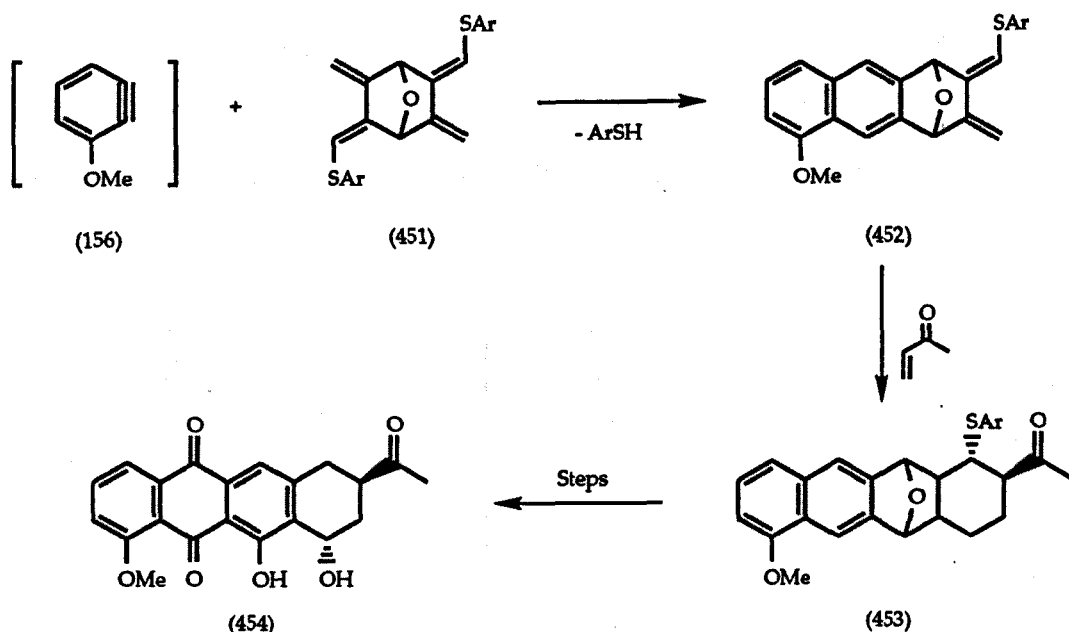
Scheme 149

Diels-Alder reactions between benzyne and acyclic dienes generally lead to poor yields of cycloadducts because the diene tends to adopt the more thermodynamically stable *trans* configuration, rather than the *cis* configuration which is required for the cycloaddition. This is illustrated in the cycloaddition between the diene (447) and *ortho*-benzyne, generated from *ortho*-fluorobromobenzene (103), where poor yields of Diels-Alder products (448; 4-6%) are obtained, along with the [2 + 2] (449; 4-6%) and ene products (450; 27-40%). The benzyne appears to be consumed before the diene can adopt an *s-cis* conformation (Scheme 150).¹⁹¹



Scheme 150

If the *s-cis* conformation of acyclic 1,3-dienes is fixed, then Diels-Alder reactions do become viable; an example of this fixed conformation is found in *ortho*-quinodimethanes, and this has been exploited in several examples of linear polyannulated ring system formation. For example, in the synthesis of 11-Deoxydaunomycinone, a suitably bridged *bis*-diene (451) is reacted with 3-methoxybenzyne (156) to give a cycloadduct (452), which is later trapped by methyl vinyl ketone to give the anthracyclinone skeleton (453). Further functional group manipulation then yields the natural product (Scheme 151).¹⁹²



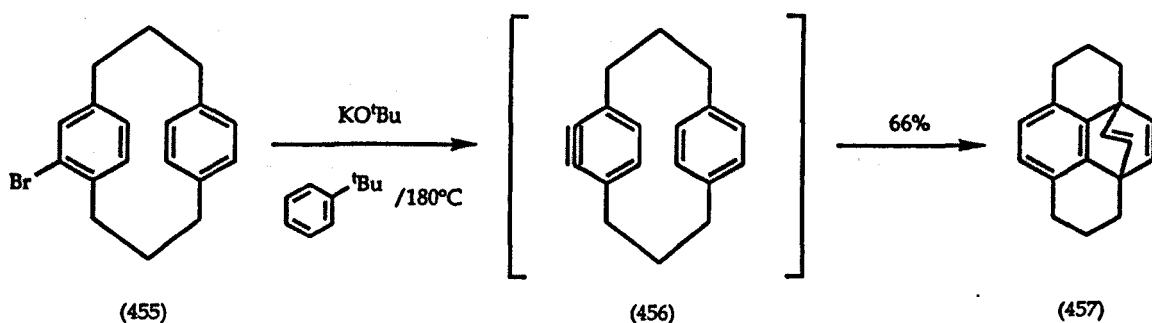
Scheme 151

Intramolecular Diels-Alder Reactions of Benzyne

Although intermolecular Diels-Alder reactions of benzyne possess inherent problems, such as competing side reactions and the lack of regioselectivity in cycloaddition, one of the ways in which these problems can be overcome is to set up intramolecular versions, where there is a distinct possibility of controlling the regioselectivity of cycloaddition. However, despite the onset of the intramolecular Diels-Alder reaction in recent years,¹⁹³ the use of benzyne as dienophiles in such reactions has, by comparison, received little attention.

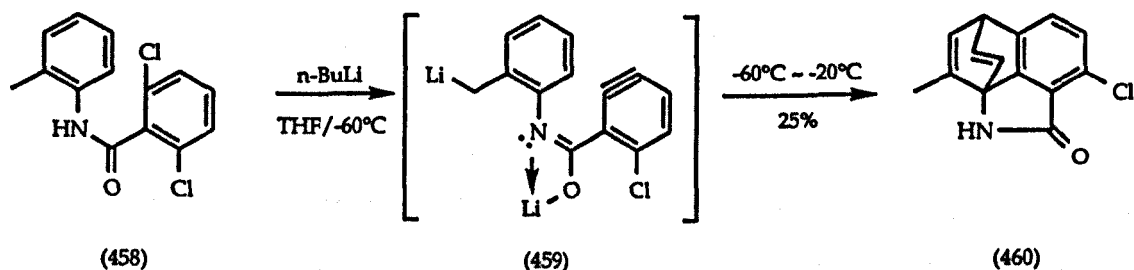
One of the first examples was reported by Longone and Gladsyz¹⁹⁴ in their synthesis of bridged benzobarrelene 5,6-dehydro[3.3]paracyclophane (457) from bromocyclophanes (455). Despite the loss of aromatisation, the rigid nature of the cyclophane system and the proximity of the rings enabled the doubly bridged benzene ring to undergo cycloaddition with the generated

benzyne to give the adduct in high yields (*Scheme 152*). A recent report by Mori *et al*¹⁹⁵ confirmed that the benzyne containing ring (e.g. in intermediate 456) undergoes rotation prior to Diels-Alder trapping by conducting their own studies on related paracyclophane ring systems.



Scheme 152

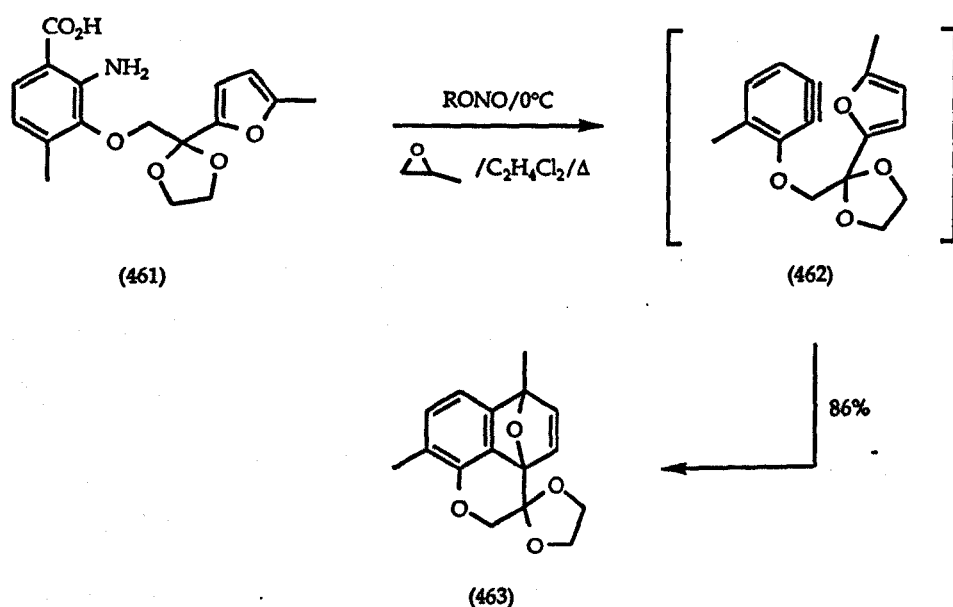
One of the first examples of an intramolecular Diels-Alder process involving only single bridging between the reacting species was reported by Houlihan *et al*¹⁹⁶ using modified Madelung conditions, where anticipated intramolecular trapping of the reactive intermediate (459) by a neighbouring benzylic group was intercepted by cycloaddition involving the two aromatic rings (*Scheme 153*).



Scheme 153

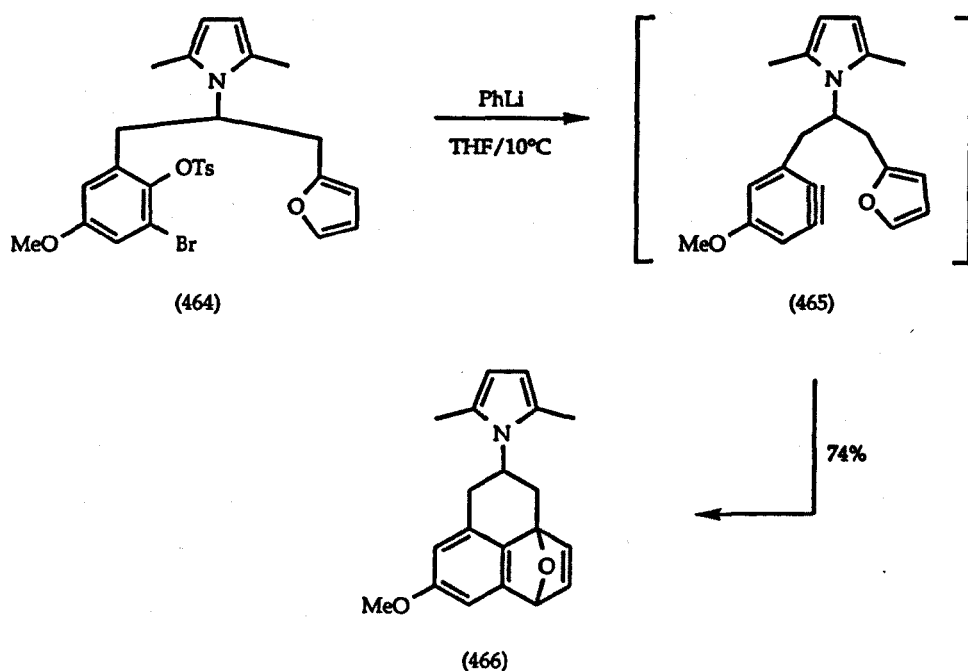
Much of the pioneering work which demonstrated that intramolecular Diels-Alder reactions of benzyne could represent a highly efficient annulative route was reported by Best and Wege when attempting

cycloadditions between singly bridged substituted benzynes and substituted furans. Using either substituted 1,2-dibromobenzenes (see *Scheme 53*) or anthranilates (461) as benzyne precursors, the synthesis of naturally occurring naphthoquinone, Mansonine E, was accomplished, where generation of the benzyne from the anthranilic acid precursor led to the synthesis of the skeleton (463) in a remarkably high yield of 86% (*Scheme 154*).⁷⁷ The potential of this route was further illustrated by the same authors in total synthesis of the naphthoquinones Mansonines I and F and Biflorin.^{85, 197}



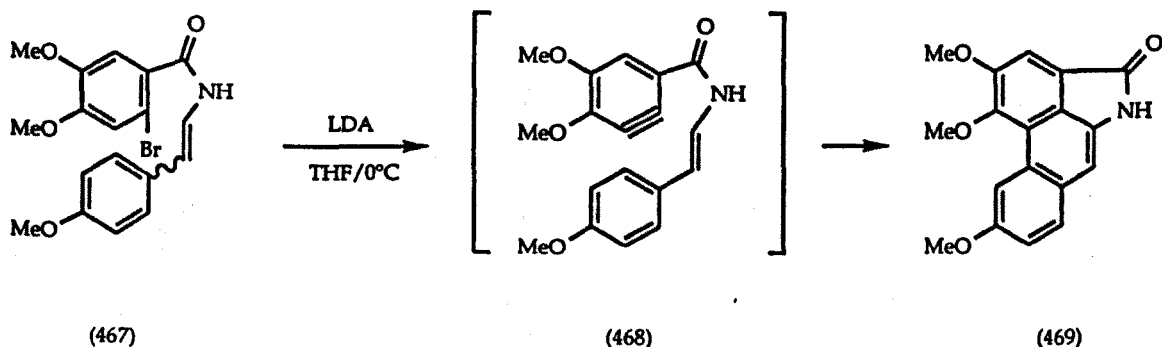
Scheme 154

Inspired by Best and Wege's studies, Szmuszkocicz and his co-workers¹⁹⁸ later reported the synthesis of 2,3-dihydro-1H-phenalene derivatives from precursors such as (464) *via* a similar intramolecular trapping of benzynes by singly bridged furans, with the skeleton (466) being subsequently converted into the substituted dihydrophenylene ring system (*Scheme 155*).



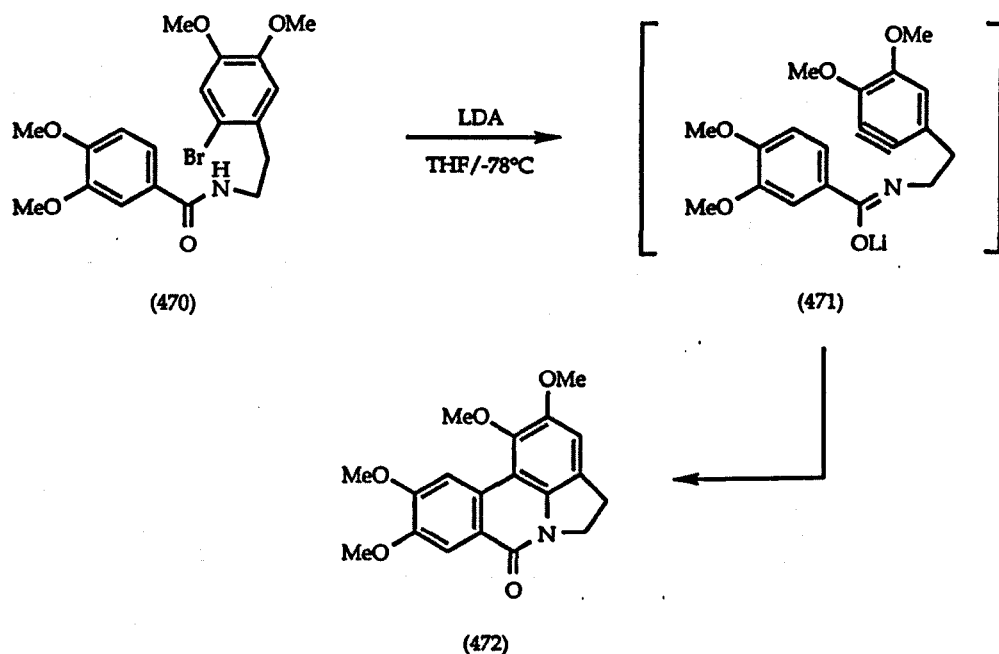
Scheme 155

Having extensively researched the area of alkaloid synthesis *via* intermolecular Diels-Alder reactions of benzyne and styrenes (see pages 98-101), Castedo and his co-workers have attempted similar syntheses in an intramolecular manner, with construction of phenanthrene ring system (*e.g.* compound 469) found in the Aristolactam alkaloids being achieved in low yields from (467) using the (*E*)-isomer of a styrylamide and a benzyne generated from an aryl bromide (Scheme 156).¹⁹⁹



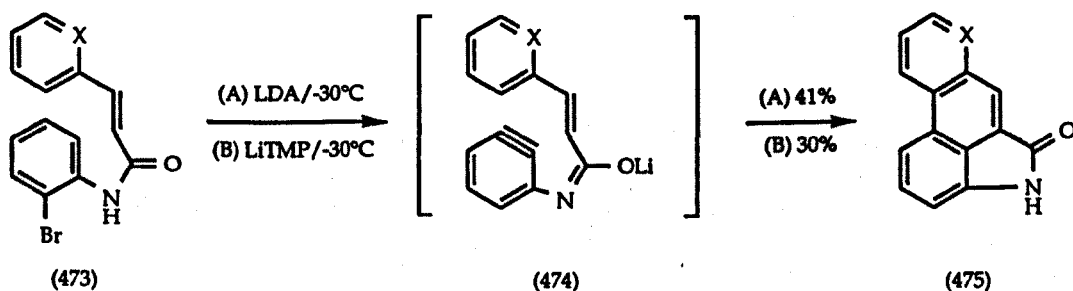
Scheme 156

A new approach to the Amaryllidaceae alkaloid ring system (472) has also been reported by Castedo,²⁰⁰ in yields comparable to those obtained in for Aristolactams synthesis (35%); by using a large excess of LDA (16 equivalents), the yield was improved to 74% (Scheme 157).



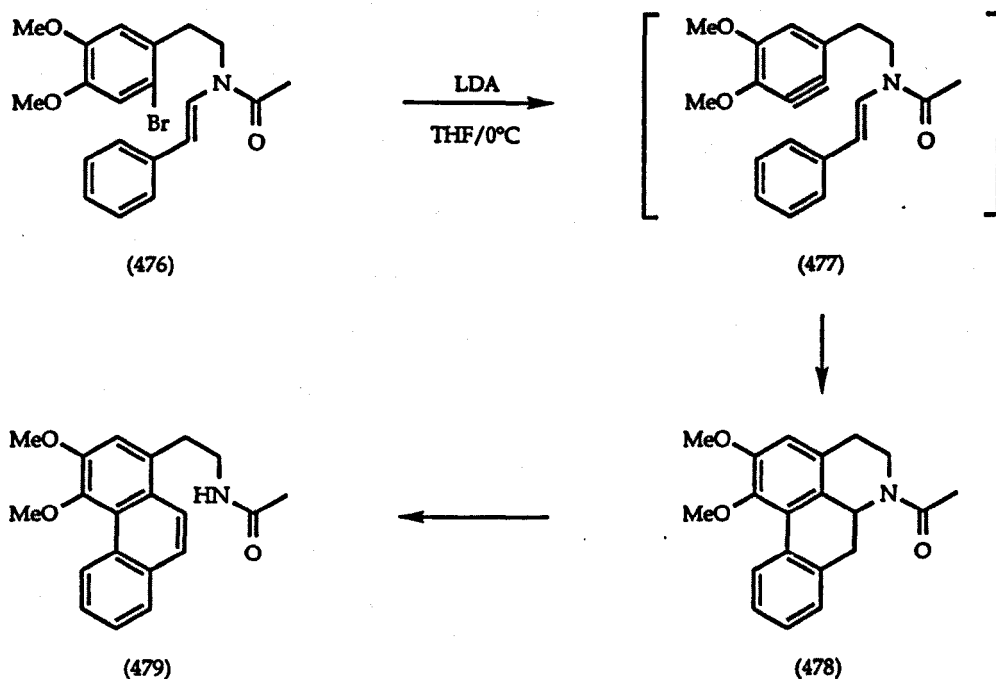
Scheme 157

The synthesis of Ergot alkaloid skeletons (475) in moderate yields has also been reported by Castedo,²⁰¹ using aryl bromides (X = CH; method A, X = N; method B) (Scheme 158).



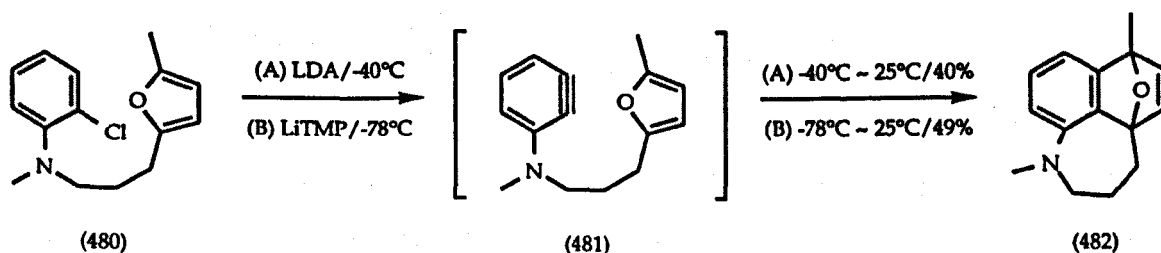
Scheme 158

Castedo extended his studies to the preparation of Aporphine alkaloids; however, instead of isolating the expected Aporphine alkaloid skeletons (478), phenanthrene species (479) were produced *via* elimination, with the yields being greatly improved (~ 60%) than those obtained for Aristolactam and Amaryllidaceae alkaloid synthesis (Scheme 159).²⁰²



Scheme 159

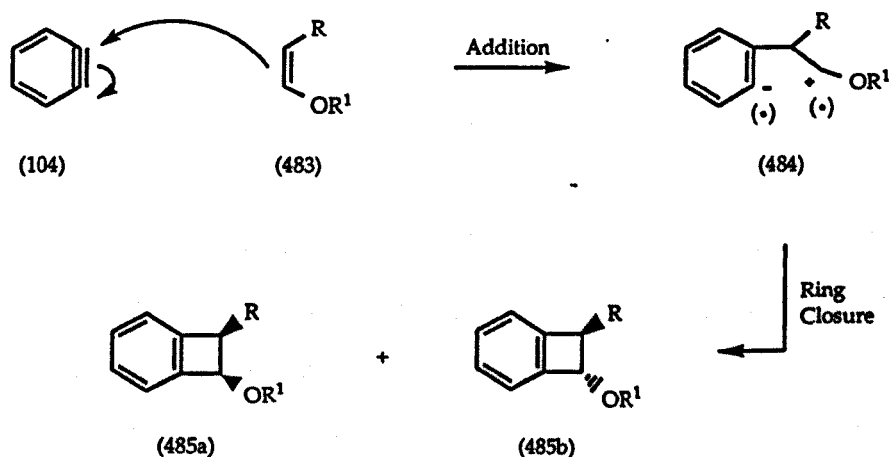
The most recent example was reported by a Japanese group²⁰³ in their construction of tetrahydrobenzazepine skeletons (482), where cycloaddition was achieved in 40-50% yields (Scheme 160).



Scheme 160

c) [2 + 2] Cycloadditions of Benzyne

Along with Diels-Alder cycloadditions, benzyne will also readily undergo [2 + 2] cycloaddition reactions with substituted alkenes, especially those which are strained and which possess electron rich carbon-carbon double bonds, leading to the formation of benzocyclobutenes.^{36, 37} Although the stereochemistry of the alkene predominates in the cycloaddition product, such cycloadditions are not stereospecific, in the sense that cycloaddition of *ortho*-benzyne with both pure *cis* and *trans* alkenes leads to both *cis* (485a) and *trans* (485b) products. This suggests that the reactions occur *via* a stepwise, non-concerted route *via* an intermediate (484) which could be dipolar or diradical in nature, and which possesses a lifetime long enough to allow bond rotation (Scheme 161).



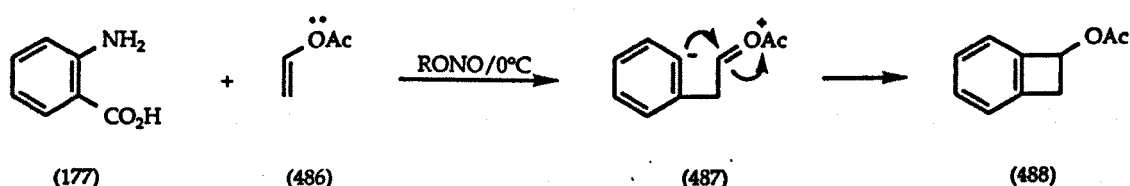
Scheme 161

There has been much discussion on the dipolar/diradical nature of the intermediate; for the addition of simple unsubstituted alkenes, the lack of rearrangements and the absence of solvent effects suggest that the intermediate possesses diradical character.²⁰⁴ In cases where alkenes are bearing strong electron donating groups such as enol ethers for example, the

first step in the cycloaddition can be considered to be a nucleophilic addition, resulting in the formation of a zwitterionic intermediate which undergoes ring closure to give the final cycloaddition product.²⁰⁵

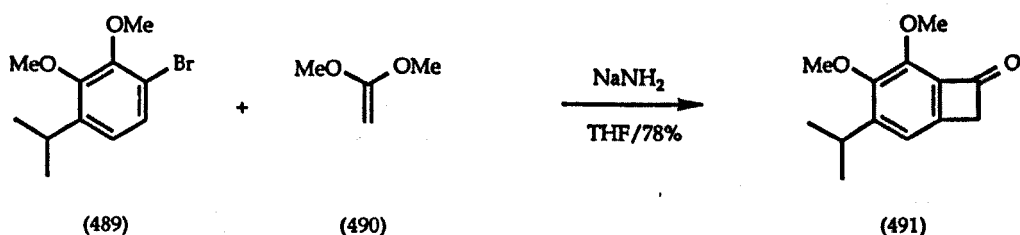
[2 + 2] Cycloadditions in Organic Synthesis¹²³

Examples of [2 + 2] cycloaddition reactions in organic synthesis are placed sporadically in the literature. Kametani *et al*²⁰⁶ have applied the synthesis of benzocyclobutenes *via* a [2 + 2] cycloaddition between benzyne and vinyl acetates (486) to the preparation of Protoberberine alkaloids (Scheme 162).



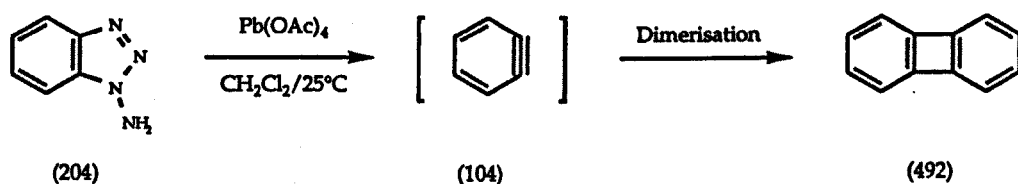
Scheme 162

Using alkenes bearing strong electron donating groups, cycloadditions have been shown to proceed in high yields, and with good regioselectivity. One example is found in the synthesis of the diterpene Taxidione,²⁰⁷ where the substituted bromoanisole (489) reacts with 1,1-dimethoxyethylene (490) to give the benzocyclobutene (491) in high yields (Scheme 163).



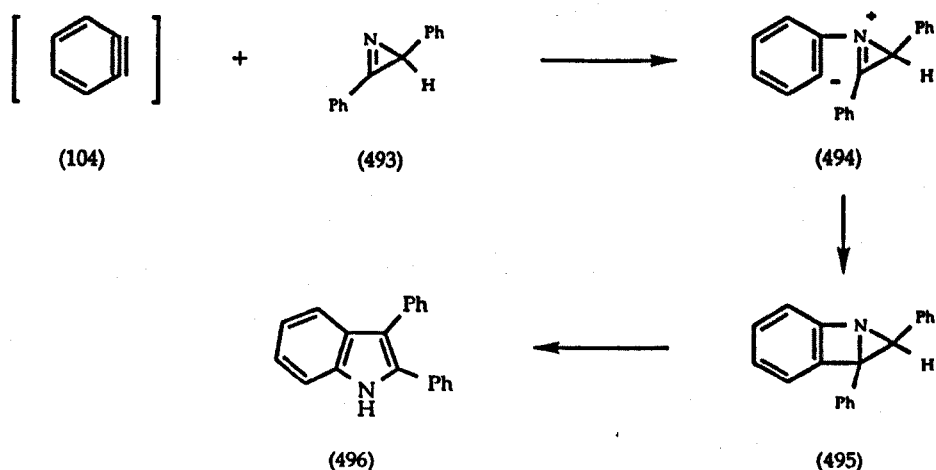
Scheme 163

Benzynes are also known to dimerise *via* a [2 + 2] cycloaddition, provided the local concentration of the reactive intermediate is high enough. Such an incidence is one of the distinguishing features of the 1-aminobenzotriazole route to benzyne (see *Scheme 72*), when the most favoured reagent, lead(IV) acetate is used.^{102a} In the absence of a suitable benzyne trap, the formation of biphenylene (492) proceeds in high yields (*Scheme 164*).



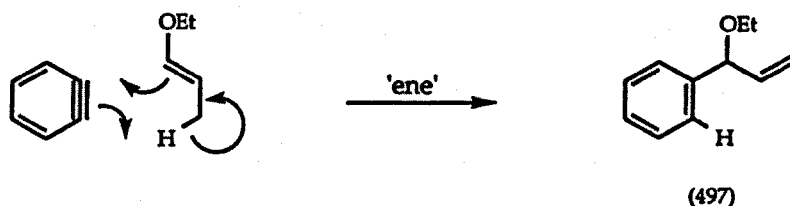
Scheme 164

The [2 + 2] cycloaddition between benzyne and heteroaromatic double bonds has been exploited in the synthesis of heterocyclic compounds; for example, the reaction of an azirine (493) with *ortho*-benzyne (104) leads to 2,3-diphenylindole synthesis (496) following ring closure and rearrangement (*Scheme 165*).²⁰⁸



Scheme 165

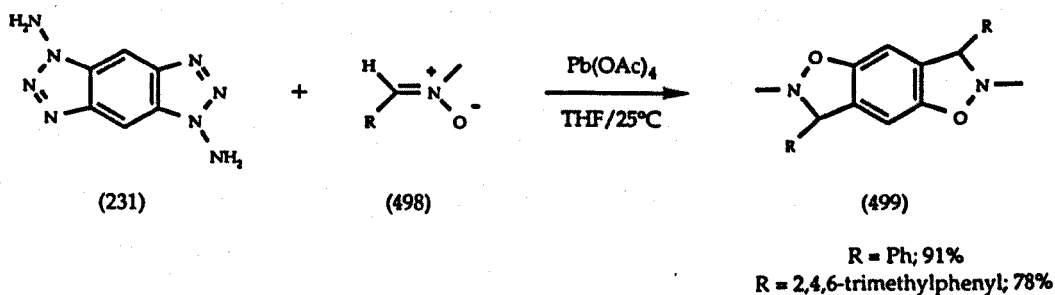
Along with Diels-Alder reactions between benzyne and acyclic 1,3-dienes (see *Scheme 150*), many [2 + 2] cycloadditions between benzyne and alkenes also proceed in reduced yields, often due to a competing and concerted 'ene' reaction which may occur if the approaching alkene possesses an allylic hydrogen and a *trans* geometry (*Scheme 166*).^{36, 37}



Scheme 166

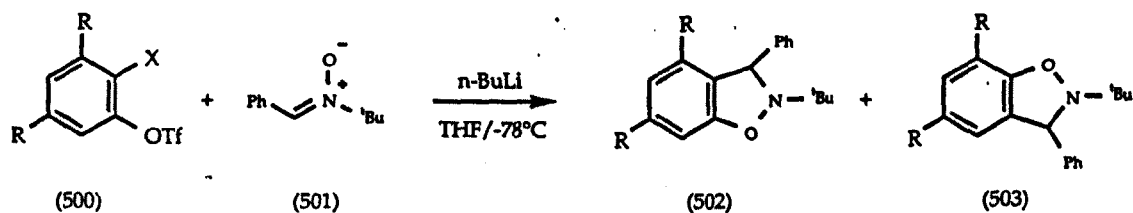
d) [1,3]-Dipolar Cycloadditions of Benzyne

As expected for such a reactive species, benzyne have also been shown to take part in [1,3]-dipolar cycloadditions with 1,3-dipolar species.^{36, 37} Since Huisgen first reported that such reactions could be carried out,²⁰⁹ this process has received surprisingly little attention, until Hart¹¹⁶ demonstrated that his 1,4-benzdiyne species, generated from the *bis*-aminobenzotriazole (231), could take part in high yielding *bis*-[1,3]-dipolar cycloadditions with nitrones (*Scheme 167*).



Scheme 167

A recent report by a Japanese group²¹⁰ has shown that unsymmetrical, polarized benzyne generated from *ortho*-haloaryltriflates (500) (X = Br, I) can be induced to take part in [1,3]-dipolar cycloadditions with nitrones, with a remarkable degree of regioselectivity. With a methoxymethyl substituent (R = OMOM), the addition of the nitron to the benzyne occurred in a totally regioselective manner to give the *syn* adduct (502; 91%). Steric effects of benzyne substituents were also studied, with the reaction of the methyl substituted precursor (R = Me) yielding a different adduct ratio (502:503 = 1:2.5) to that obtained using the more bulky *t*-butyl (R = *t*-Bu) substituent (502:503 = 2.3:1). Trialkylsilyl substituents possessing even more electron donating properties, such as the trimethylsilyl (R = TMS; 502:503 = 1:10) and *t*-butyldimethylsilyl (R = TBDMS; 502:503 = 1:8) groups led to greater regioselectivity (Scheme 168).



Scheme 168

e) Summary

From the examples which have been outlined in Chapters Three and Four, it can be seen that benzyne could have a potentially widespread and useful role to play in organic synthesis, but for the difficulties associated with precursor preparation, the use of nucleophile-derived reagents, and the exceptionally high reactivity of the reactive intermediate in each case. However, in the case of both intramolecular nucleophilic trapping, and especially cycloaddition reactions, where the reacting partners are brought

into close proximity and regioselectivity is determined, then benzyne can serve as extremely valuable synthetic intermediates, taking part in generally high yielding and regioselective annulations. If the emerging use of non-nucleophilic reagents for benzyne generation can become fully exploited, then more efficient routes to benzyne may result in a greater role to play for these reactive intermediates in synthetic organic chemistry.

CHAPTER FIVE

Preliminary Studies of Novel Benzyne Chemistry

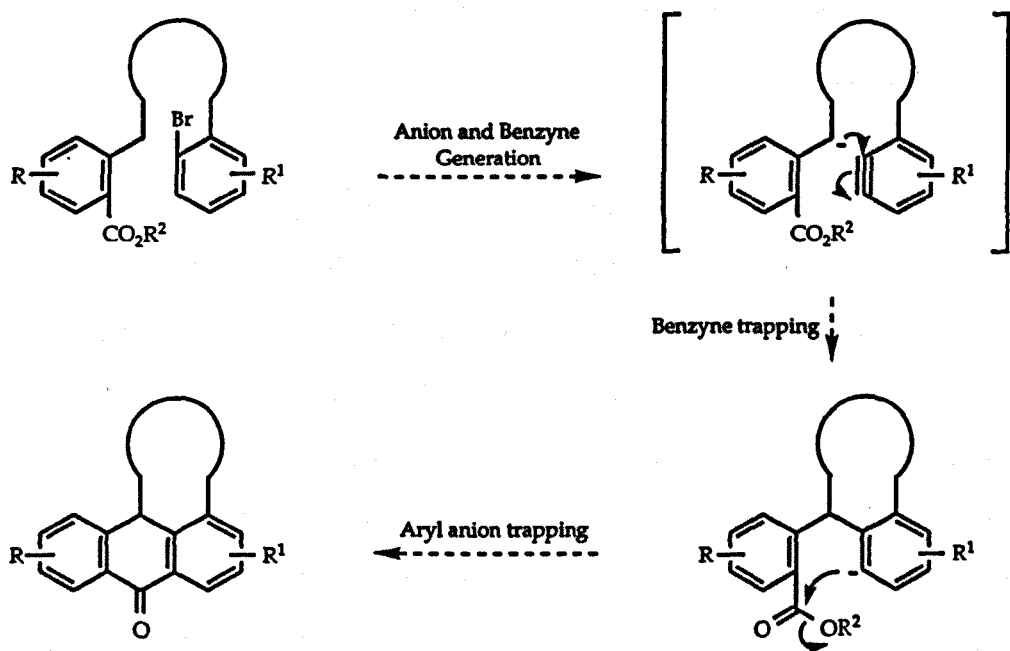
- a) *Introduction*
- b) *Intramolecular Non-Concerted Benzyne Cyclisations*
- c) *Intramolecular Diels-Alder Reactions of Benzyne*

a) Introduction

Although intermolecular and intramolecular annulations of benzyne have been applied in numerous instances (see Chapters Three and Four), previously mentioned difficulties associated with both the synthesis of substituted benzyne precursors and their subsequent reactions have resulted in their lack of exploitation of benzyne in organic synthesis, compared to other classical reactive intermediates. Therefore, in an attempt to correct this imbalance, and at the same time maintain our groups' interest in the utilisation of reactive intermediates in heterocyclic annulations, our attention switched from studying *ortho*-quinodimethanes to developing some novel benzyne chemistry. One particular aspect that warranted further investigation was the application of intramolecular nucleophilic/cycloaddition reactions to the synthesis of polycyclic ring systems, thus exploiting the inherent entropic and regioselective advantages over the intermolecular equivalent.

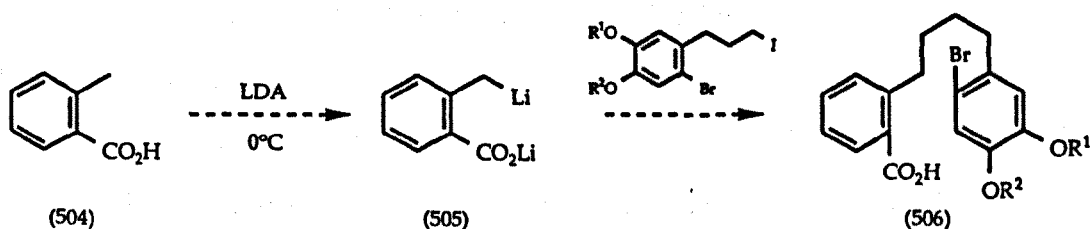
b) Intramolecular Non-Concerted Benzyne Cyclisations

Our initial investigations focussed on developing an intramolecular equivalent of the 1,4-dipolar addition of nucleophiles to benzyne, which had already been exemplified by Biehl, amongst others, in the synthesis of anthraquinones (see Chapter Three). Here, the construction of an anthraquinone-type precursor was envisaged, which upon exposure to basic conditions would simultaneously generate a carbanionic species and the benzyne. Trapping of the benzyne by the carbanion would result in an initial annulation, and nucleophilic attack of the resulting aryl anion onto the neighbouring carbonyl group would complete the process (*Scheme 169*).



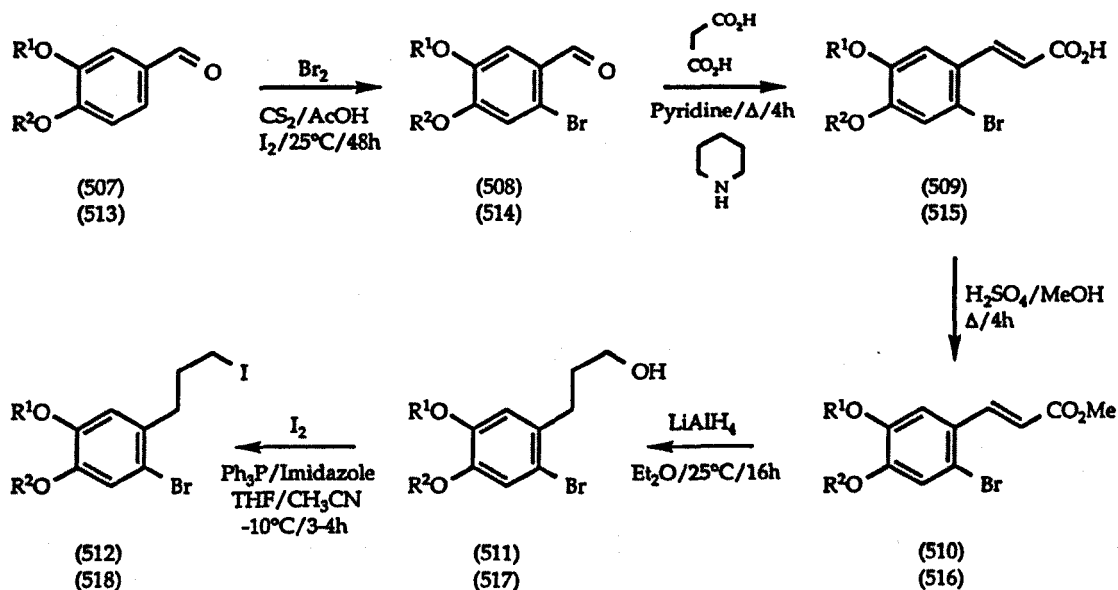
Scheme 169

Construction of the annulation precursors appeared to be possible *via* the functionalisation of *ortho*-toluic acid (504) with benzyne precursors that would be suitably substituted, so as to eliminate problems concerning the regiospecificity of benzyne generation (Scheme 170). Functionalisation of this acid had been previously reported by Creger,²¹¹ who had shown that the generation of the dianion (505) from the acid could be effected upon exposure to two equivalents of LDA at 0°C, with subsequent alkylation of the dianion with electrophiles such as *n*-bromobutane being achieved in good yields.



Scheme 170

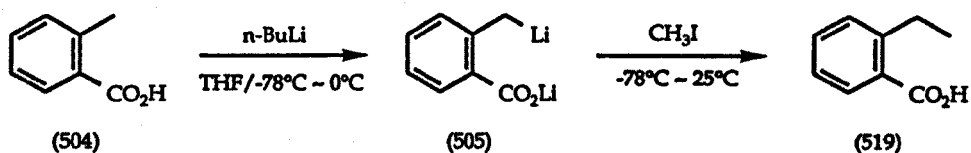
Synthesis of the suitably substituted benzyne precursors was attempted *via* a five step process starting from either commercially available 3,4-dimethoxybenzaldehyde (507; $R^1 = R^2 = \text{CH}_3$) or piperonal (513; $R^1 + R^2 = \text{CH}_2$) (Scheme 171). Thus, bromination of 3,4-dimethoxybenzaldehyde was achieved upon stirring with one equivalent of bromine in glacial acetic acid containing carbon disulphide and a catalytic trace of iodine at ambient temperature, with the product (508) isolated as a white powder in 68% yield. Knoevenagel condensation of this aldehyde with malonic acid gave the cinnamic acid (509) as a brown powder in 70% yield; subsequent esterification of this acid gave the methyl cinnamate (510) as a white solid in 68% yield. Reduction of the methyl cinnamate to give the saturated alcohol (511) was carried out upon vigorous stirring with lithium aluminium hydride in diethyl ether at ambient temperature, with the product isolated as a semi-solid material in 71% yield. One step iodination²³ of this alcohol using molecular iodine in the presence of triphenylphosphine and imidazole using THF/acetonitrile as the solvent gave the expected iodide (512) as a pale yellow oil, albeit in a poor yield of 32%, which was a consequence of loss of this material through poor handling. Preparation of the other iodide (518) was achieved in a similar manner starting from piperonal, with bromination under similar conditions to before leading to the formation of 2-bromopiperonal (514) as an off-white powder in 87% yield. Knoevenagel condensation of this aldehyde with malonic acid yielded the cinnamic acid (515) as a yellow powder in a good yield of 75%; esterification of this material gave the methyl ester (516) as a yellow powder in 65% yield. Reduction of the ester using lithium aluminium hydride led to the formation of the alcohol (517) as an orange-yellow semi-solid in 55% yield, and one step iodination of the alcohol yielded the iodide (518) as a yellow oil in a 65% yield.



Scheme 171

Attempted generation of the dianion (505) from *ortho*-toluic acid (504) using LDA at 0°C , followed by the addition of the iodides (512) and (518) led to a very slow dissipation of the red colouration, associated with the dianion, over a period of several hours, and spectroscopic analysis of the isolated crude material showed virtually no alkylation of the starting material. Though not proven, the apparent lack of dianionic reactivity could be attributed to an observation made by Creger, who suggested that the failure of the dianion to react with certain alkyl halides and deuterium oxide was a consequence of complexation between the dianion and diisopropylamine. A similar complexation could be used in the present cases to explain the failure when using the iodides (512 and 518).

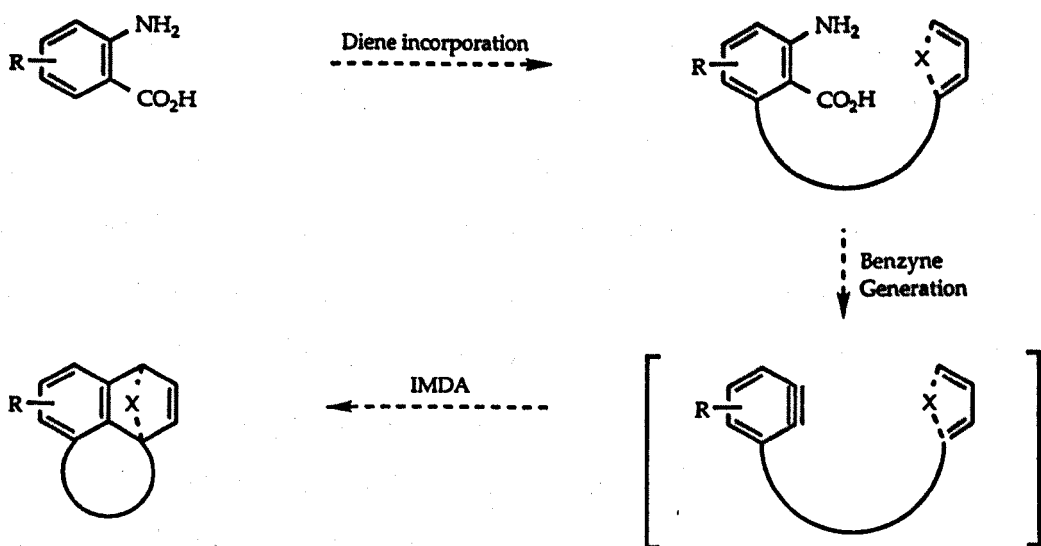
Although an improved and more effective procedure of dianion (505) formation using *n*-butyllithium at -78°C , followed by warming to 0°C had been reported by Belletier and Spletzer (Scheme 172),²¹² attempts to repeat our reactions under these conditions resulted in a similar failure to generate the dianion. Consequently, our attention switched to other lines of work.



Scheme 172

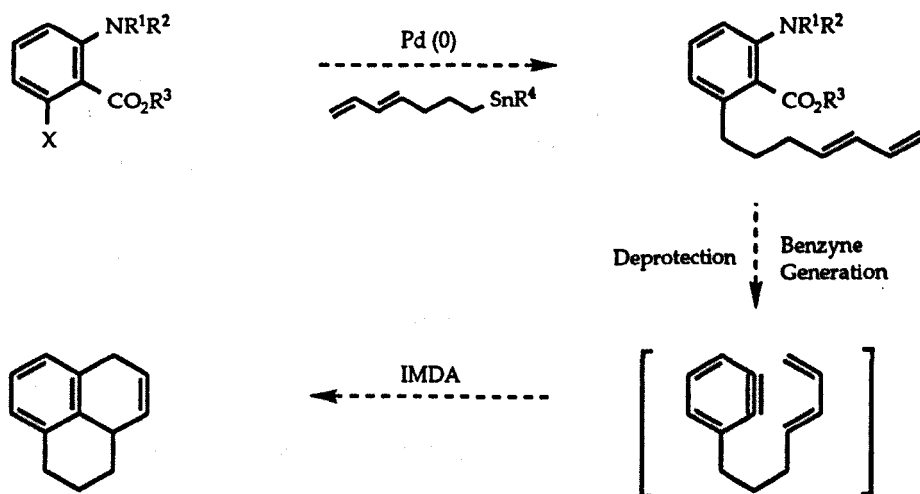
c) Intramolecular Diels-Alder Reactions of Benzyne

With the synthesis of fused polycyclic compounds *via* the intramolecular Diels-Alder cycloaddition [IMDA] of benzyne still being a relatively new annulation procedure, our attention focussed upon exploring this underexploited area. A suitable choice of precursor appeared to be *ortho*-substituted anthranilates, which had been shown to take part in IMDA reactions in an efficient manner by Wege, when using furans as 1,3-diene counterparts.^{77, 85, 197} Accordingly, our main target was to construct such species (using either acyclic or cyclic 1,3-dienes), with the primary aim being the development of novel chemistry for their construction (Scheme 173).



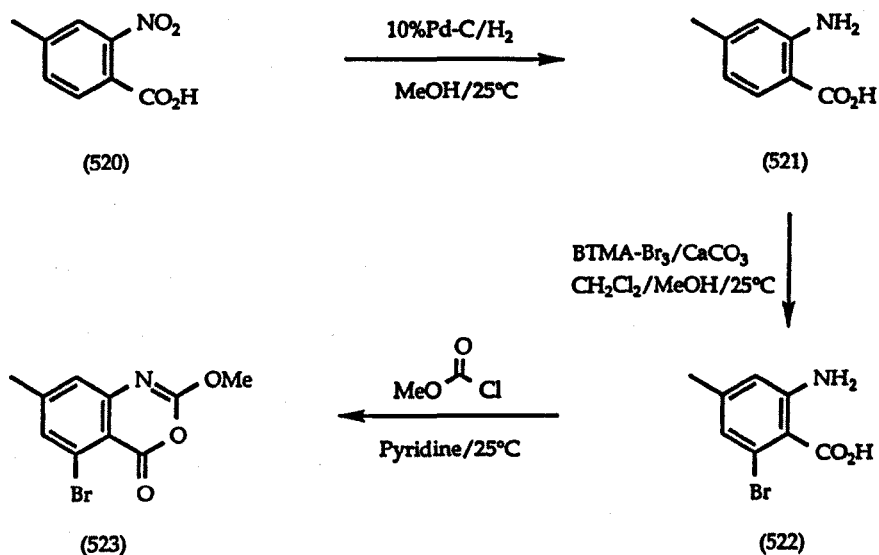
Scheme 173

A suitable route to *ortho*-substituted anthranilates which was initially considered concerned the utilisation of palladium(0)-catalysed coupling chemistry in the coupling of halogenated anthranilates ($X = \text{Br}, \text{I}$) with stannylated 1,3-diene containing species (Scheme 174).



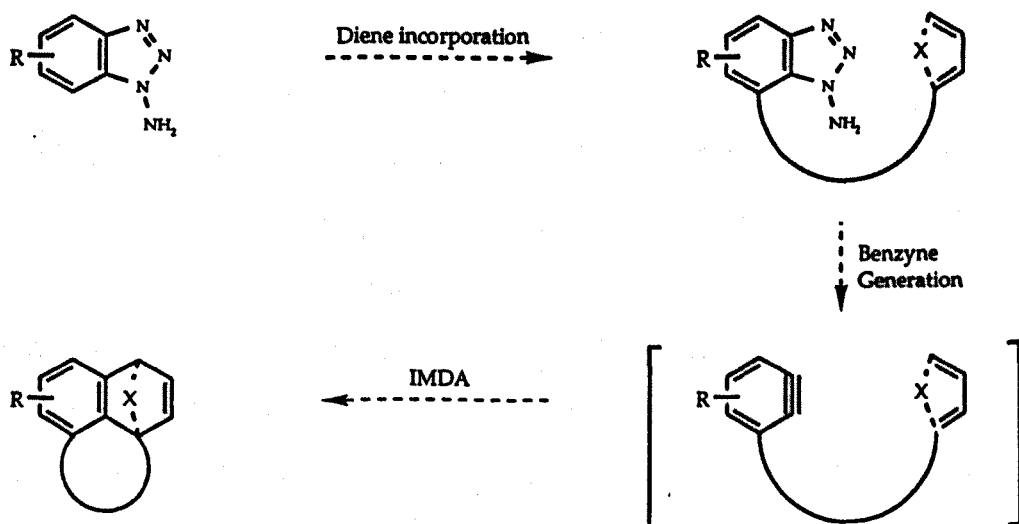
Scheme 174

Construction of suitably protected *ortho*-bromoanthranilic acid (523) was attempted starting from commercially available 5-methyl-2-nitrobenzoic acid (520) (Scheme 175). Initial attempts at reducing the acid using standard Sn/HCl conditions²¹³ yielded 5-methylanthranilic acid (521) as light yellow needles in a poor yield of 26%. Switching to an atmosphere of hydrogen in the presence of 10% Pd-C catalyst at ambient temperature improved the yield to a respectable 65%. Bromination of the anthranilic acid was effected by stirring with benzyltrimethylammonium tribromide [BTMA-Br_3],²¹⁴ with the brominated anthranilic acid (522) being isolated as a brown amorphous solid in quantitative yield. Protection of the anthranilic acid, in anticipation of the coupling step, appeared possible by converting to a 4*H*-3,1-benzoxazin-4-one (523).²¹⁵ However, failure to accomplish this step in yields greater than 10-15% spelled the end for this scheme.



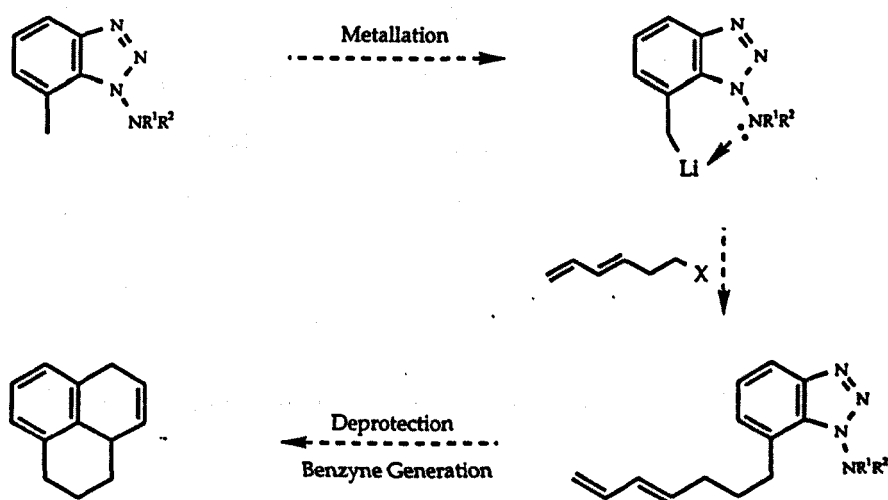
Scheme 175

Turning our attention to using alternative benzyne precursors in the IMDA process, the absence of many applications of the 1-aminobenzotriazole route to benzyne to organic synthesis inspired us to consider the possibility of constructing *ortho*-substituted 1-aminobenzotriazoles, and utilising these species in a similar manner to using *ortho*-substituted anthranilic acids (Scheme 176).



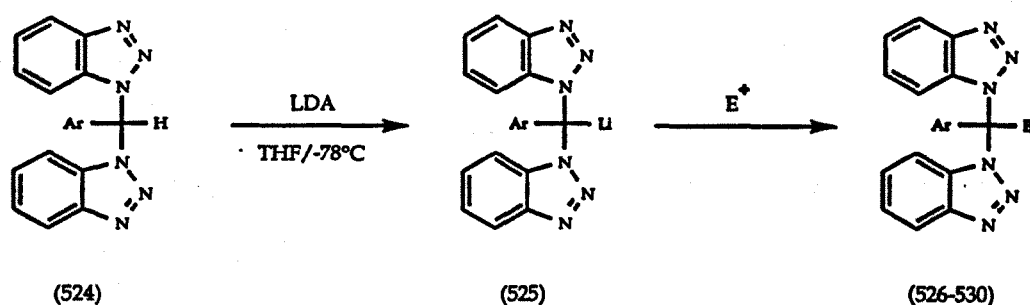
Scheme 176

For the construction of *ortho*-substituted 1-aminobenzotriazoles, the amine group appeared to be well placed to facilitate deprotonation of either an adjacent benzylic sp^3 or aromatic sp^2 centre, with the anionic intermediate being alkylated to incorporate the 1,3-diene (Scheme 177).²¹⁶ The choice of functionalising benzylic sp^3 centres, and not aromatic sp^2 centres arose from numerous observations that benzylic sp^3 centres generally lead to high yielding alkylations because of their greater nucleophilicity, compared to related sp^2 centres, which tend to react relatively poorly with alkylating agents in general.²¹⁷



Scheme 177

Although no examples of the metallation of 1-aminobenzotriazole or its derivatives had been previously reported, strong evidence that this heterocyclic ring system would be stable to organolithium bases was put forward in the form of reported metallations on closely related systems. Extensive studies on the metallation of analogous *N*-substituted benzotriazoles (524) have been reported by Katritzky and co-workers, for example, in the synthesis of aromatic ketones, diketones and α -hydroxyketones (Scheme 178; Table 3).²¹⁸

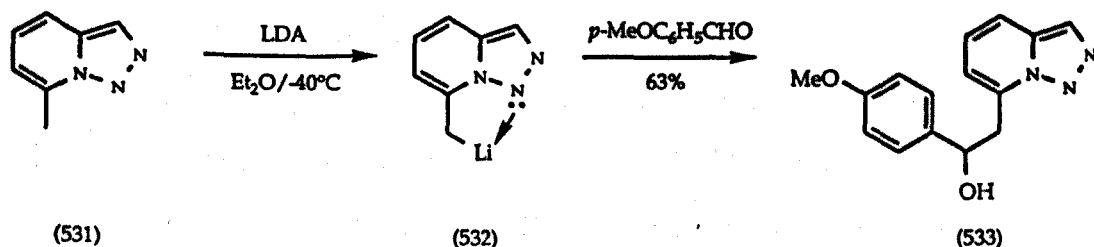


Scheme 178

<u>ELECTROPHILE</u>	<u>PRODUCT</u>	<u>YIELD (%)</u>
CH ₃ I	(526)	92
CH ₃ (CH ₂) ₃ Br	(527)	78
CH ₂ :CHCH ₂ Br	(528)	84
C ₆ H ₅ COCl	(529)	61
C ₆ H ₁₀ O	(530)	78

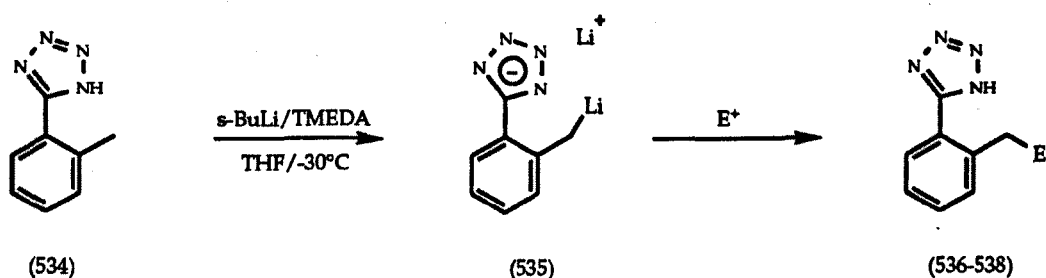
Table 3; Alkylation of N-Substituted Benzotriazole (524)

Analogous metallation of 7-substituted 1,2,3-triazolo[1,5-a]pyridines (531) was reported by Jones, with the *peri*-nitrogen on the triazole ring probably facilitating deprotonation of the methyl substituent on the neighbouring pyridine ring (Scheme 179).²¹⁹



Scheme 179

One final example which illustrated nitrogen heterocycle stability towards organolithium bases was reported by Flippin,²²⁰ in his studies on the metallation of 5-aryltetrazoles (534), with the tetrazole ring facilitating in the lithiation of the adjacent methyl substituent leading to good yields of alkylated products (Scheme 180; Table 4).



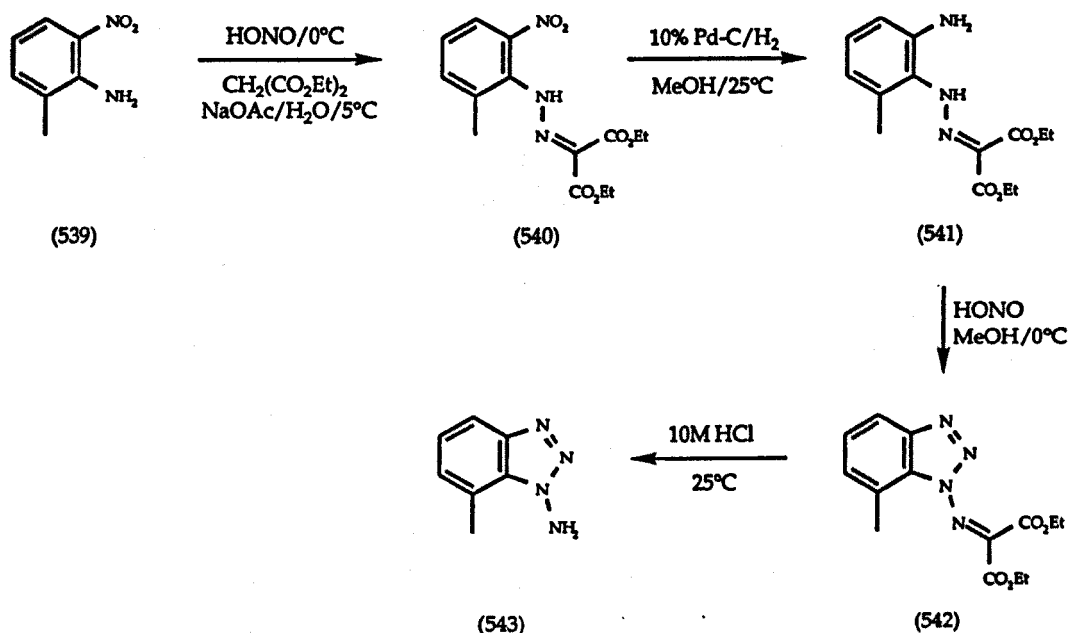
Scheme 180

<u>ELECTROPHILE</u>	<u>PRODUCT</u>	<u>YIELD (%)</u>
CH_3I	(536)	71
$\text{CH}_3(\text{CH}_2)_4\text{I}$	(537)	92
$\text{C}_6\text{H}_5\text{CH}_2\text{Br}$	(538)	73

Table 4; Functionalisation of 5-Aryl Tetrazole (534)

During their pioneering studies of benzyne generation, Campbell and Rees reported the synthesis of 1-aminobenzotriazoles and some simple derivatives in four steps, starting from appropriately substituted *ortho*-nitroanilines. Amongst the derivatives synthesized was the substituted analogue, 7-methyl-1-aminobenzotriazole (543), a substrate which was suitable for our studies (Scheme 181).^{102a} Thus, commercially available 2-methyl-6-nitroaniline (539) was diazotised under standard conditions (NaNO_2 , HCl , 0°C), and the diazonium species added dropwise to a

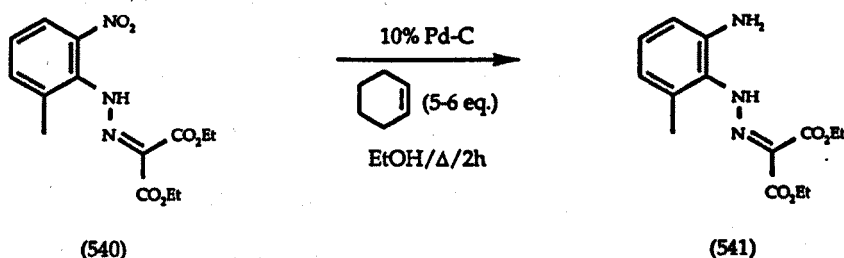
vigorously stirred, buffered (sodium acetate) emulsion of diethyl malonate and water at 5°C. Filtration of the resulting suspension and recrystallisation of the crude material yielded the nitro-iminomalonate (540) as a red-orange powder in a moderate 45-55% yield.



Scheme 181

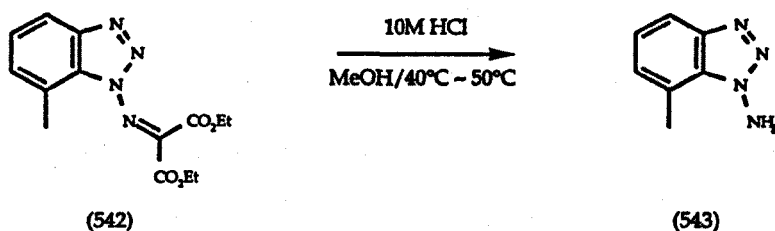
Attempts at reducing the nitro group of the iminomalonate (540) under an atmosphere of hydrogen using methanol as solvent with a catalytic amount of 10% Pd-C at ambient temperatures led to the isolation of inseparable mixtures of the starting material and the desired product (541). Switching to high pressure hydrogenation, typically at 80 atm, led to complete removal of the starting material, with the required aniline retrieved from the solvent as orange needles, albeit in poor yields of 40-50%. As high pressures were leading to the loss of substantial amounts of the product, an alternative procedure of reducing the aromatic nitro group was sought. One notable method developed by Johnstone *et al* involved the reduction of such species *via* a transfer hydrogenation procedure, where

cyclohexene is used as the hydrogen source.²²¹ Hence, reduction of the nitroiminomalonate was attempted, with the substrate being treated with an excess of cyclohexene and a catalytic amount of 10% Pd-C in refluxing ethanol. Isolation of the aniline (541), as clean orange crystals in improved yields of 70-75%, was achieved by simple filtration and cooling of the ethanolic solution (*Scheme 182*).



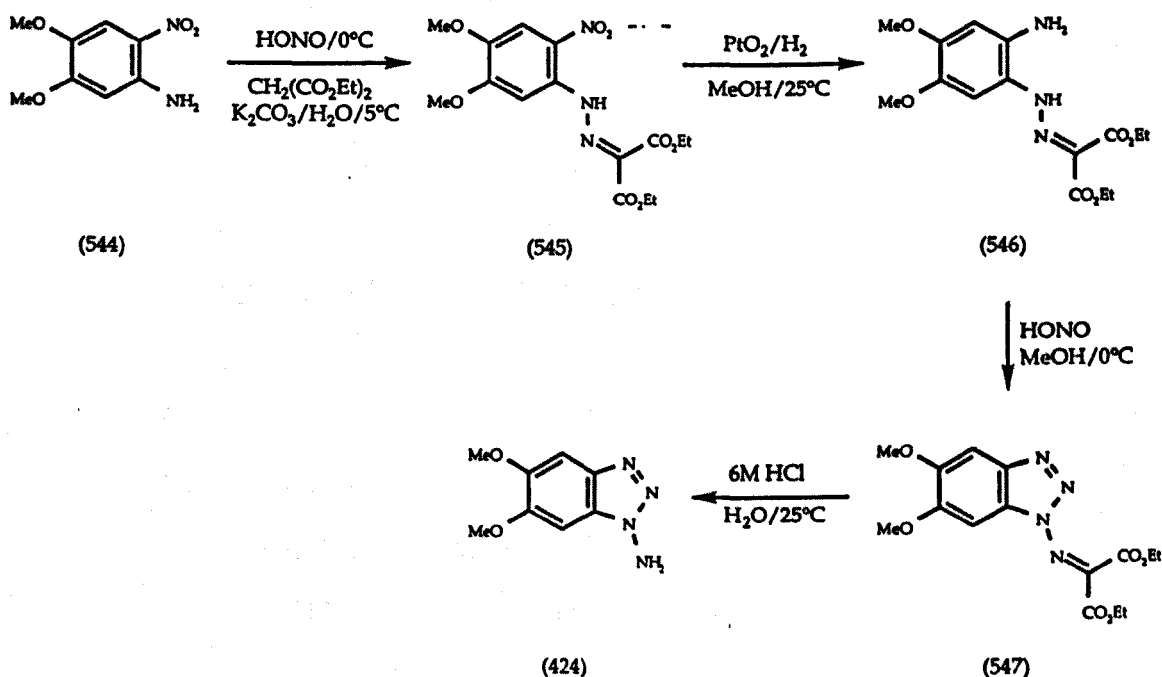
Scheme 182

Diazotisation of the aniline (541) under standard conditions led to the formation of the malonyl protected 7-methyl-1-aminobenzotriazole (542), which was isolated as an amorphous light yellow solid in high yields of 90-95% after recrystallisation. Removal of the malonate group *via* acidic hydrolysis using concentrated hydrochloric acid at ambient temperatures as previously recommended yielded low quantities of 7-methyl-1-aminobenzotriazole (543) (10-25%); this drawback was overcome by repeating the hydrolysis using methanol as a co-solvent, with gradual heating of the mixture to 40-50°C being required for the complete consumption of the starting material. Upon removal of the solvent and neutralisation of the aminobenzotriazole salt using sodium carbonate, the free aminobenzotriazole was isolated as an amorphous white powder in greatly improved yields of 75-85% after recrystallisation, thus supplying us with plenty of substrate for our key studies.



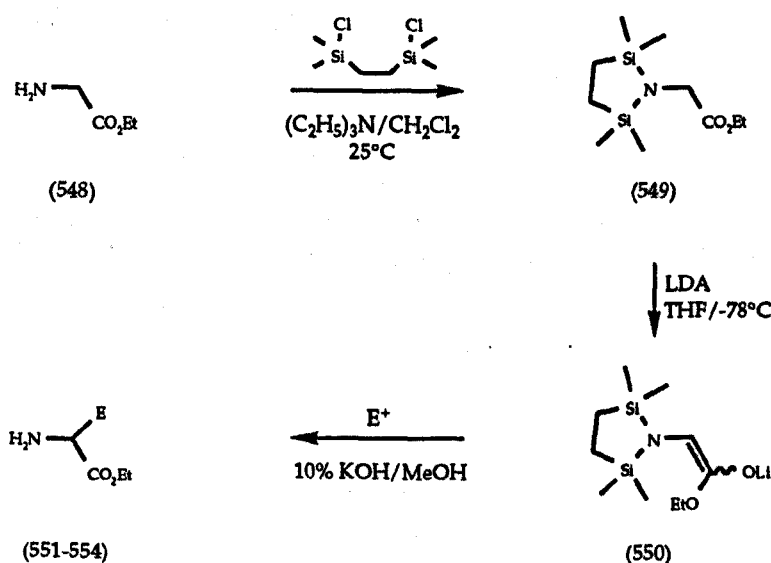
Scheme 183

The modifications that were made in overcoming the problems in the synthesis of 7-methyl-1-aminobenzotriazole (543) were not unique to our studies; in their attempted synthesis of the analogous benzyne precursor 5,6-dimethoxy-1-aminobenzotriazole (424), Rigby and Holsworth also made several modifications to Campbell and Rees' procedure, including using potassium carbonate as the buffer in the synthesis of the malonate (545) instead of sodium acetate, and the use of platinum oxide, instead of 10% Pd-C, as the catalyst in the hydrogenation of the nitro group to give the aniline (546) (*Scheme 184*).¹⁸⁵



Scheme 184

The next stage in our studies was to derivitise the amine group in 7-methyl-1-aminobenzotriazole (543) with a protecting group that could be incorporated and removed under mild conditions, and which would also be stable to organolithium bases. Magnus *et al* reported that tetramethyldisilylazacyclopentane [STABASE] adducts, generated *via* the protection of primary amines such as ethyl glycinate (548) with 1,1,4,4-tetramethyl-1,4-dichlorodisilylthane, could be used for such a process (Scheme 185; Table 5).²²²

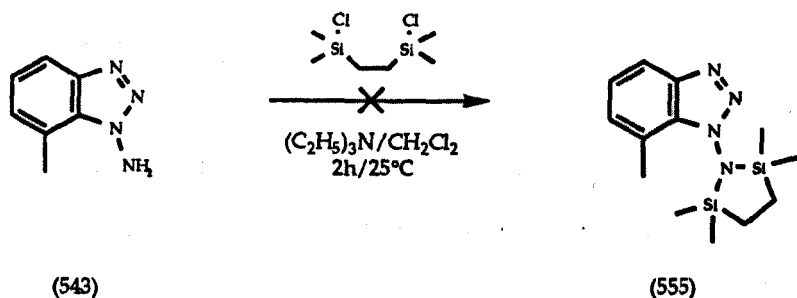


Scheme 185

<u>ELECTROPHILE</u>	<u>PRODUCT</u>	<u>YIELD (%)</u>
CH ₃ I	(551)	89
CH ₂ CH:CH ₂ Br	(552)	91
C ₆ H ₅ CHO/(CH ₃) ₃ SiCl	(553)	85
(CH ₃) ₃ CCH ₂ Br	(554)	80

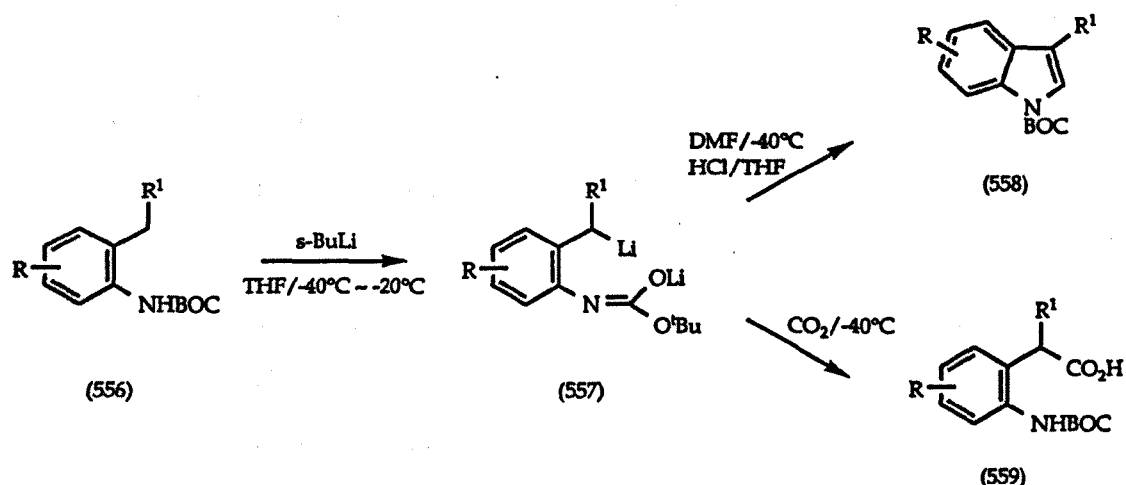
Table 5; Alkylation of Lithiated STABASE Adduct (550)

Generation of the STABASE adduct of 7-methyl-1-aminobenzotriazole (555) following Magnus's procedure was attempted by the addition of one equivalent of 1,1,4,4-tetramethyl-1,4-dichlorodisilylthane and triethylamine to a stirred solution of the substrate (543) in dichloromethane at ambient temperature (Scheme 186). However, spectroscopic analysis of the crude material isolated upon work-up showed that protection had completely failed to occur, with total recovery of the starting material. Despite being able to repeat the formation of the STABASE adduct of ethyl glycinate (549) in 80% yield, failure to protect the aminobenzotriazole resulted in a continued search for a suitable protecting group.



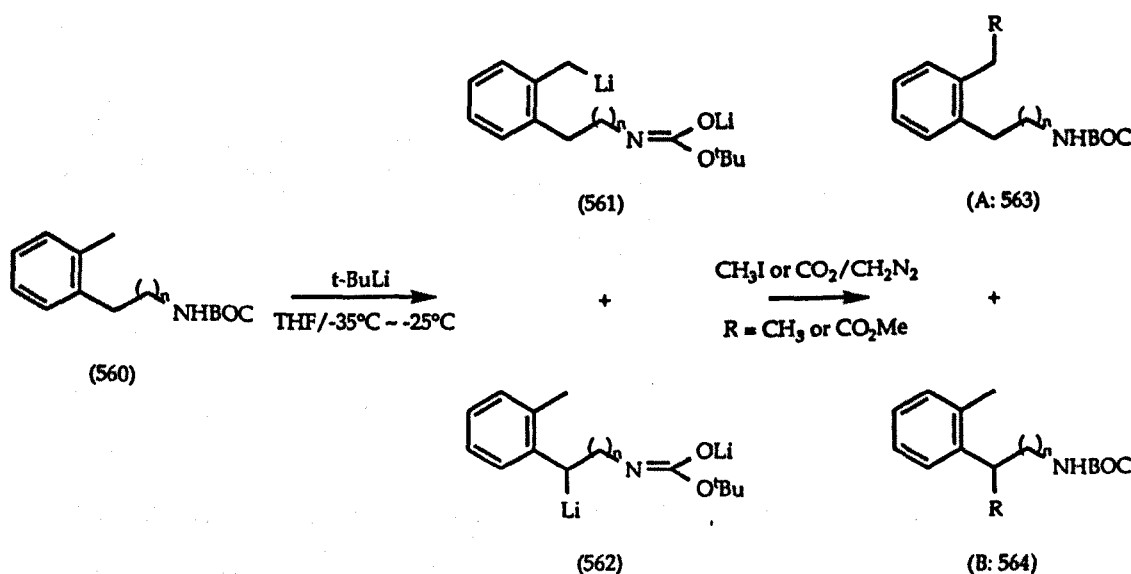
Scheme 186

One particular amine protecting group which has been extensively used in facilitating deprotonation of aromatic sp^2 and benzylic sp^3 sites and which appeared to be suitable for our purposes was the *tert*-butoxycarbonyl [BOC] group.^{223, 224} For the deprotonation of benzylic sp^3 centres, which was required in our projected studies, Clark *et al* reported the directed deprotonation of the benzylic methyl group in BOC-protected *ortho*-toluamide (556) during the course of their studies on indole/oxindole synthesis. Generation of the dianion intermediate (557) was accomplished upon exposure to *sec*- or *tert*-butyllithium at temperatures between - 20 and - 40°C (Scheme 187).²²⁴



Scheme 187

Clark *et al* later extended their studies to the potential for using the BOC group as a remote directing group for the metallation of benzylic sp^3 groups by investigating the effect of chain length between the BOC group and the aromatic ring. Deprotonation of the methyl substituent was effected efficiently for examples for up to $n = 3$, whilst for $n = 2$ the directing group appeared to be well positioned to aid deprotonation of the benzylic methylene group (Scheme 188; Table 6).²²⁵

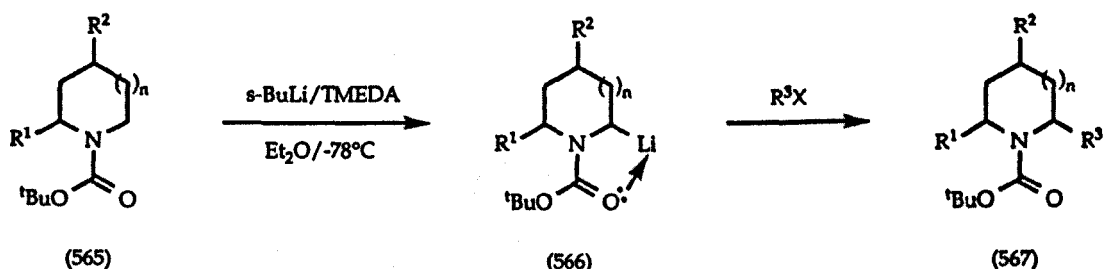


Scheme 188

<u>n</u>	<u>ELECTROPHILE</u>	<u>YIELD (%)</u>	<u>RATIO (A: B)</u>
1	CH ₃ I	80	100:0
	CO ₂ /CH ₂ N ₂	67	100:0
2	CH ₃ I	82	80:20
	CO ₂ /CH ₂ N ₂	45	80:20
3	CH ₃ I	40	100:0
	CO ₂ /CH ₂ N ₂	38	100 0

Table 6; Effect of Remote BOC Groups

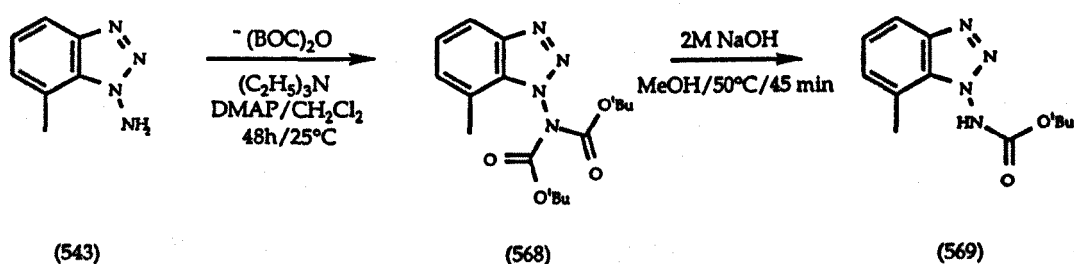
Extensive studies on the BOC-directed deprotonation of methylene sites in cyclic amides (565) have been conducted by Beak *et al* in the synthesis of single or separable diastereoisomeric substituted BOC pyrrolidines ($n = 0$), piperidines ($n = 1$) and hexahydroazepines ($n = 2$) (Scheme 189).²²⁶ The BOC group in this case acts as an adjacent directing group in an α' -lithiation process, compared to Clark's studies, in which this group acts as a remote directing group in a β -lithiation process.



Scheme 189

Standard BOC-protection of 7-methyl-1-aminobenzotriazole (543) was attempted using di-*tert*-butyl dicarbonate [(BOC)₂O] in dichloromethane in the presence of triethylamine and catalytic 4-dimethylaminopyridine

[DMAP] at ambient temperature.²²⁷ Under these conditions, tlc analysis indicated that protection was failing to go to completion, and that in order to effect complete removal of the starting material, the addition of an extra equivalent of both (BOC)₂O and triethylamine was required. Upon work-up, spectroscopic analysis of the crude material confirmed that two equivalents of the BOC group had been incorporated into the 1-aminobenzotriazole ring system, leading to the formation of the *bis*-adduct (568) as an amorphous white powder in 89% yield. Further evidence for double incorporation of the BOC group came from Fast Atom Bombardment Mass Spectrometry, where a molecular ion peak ($M^+ + H = 349$) corresponding to the *bis*-adduct was present. Fortunately, selective removal of one of the BOC groups was effected in a facile manner by mild basic hydrolysis using 2M sodium hydroxide with methanol as a co-solvent at 50°C; the desired mono BOC protected 7-methyl-1-aminobenzotriazole (569) was isolated in virtually quantitative yield as an amorphous white powder (Scheme 190).



Scheme 190

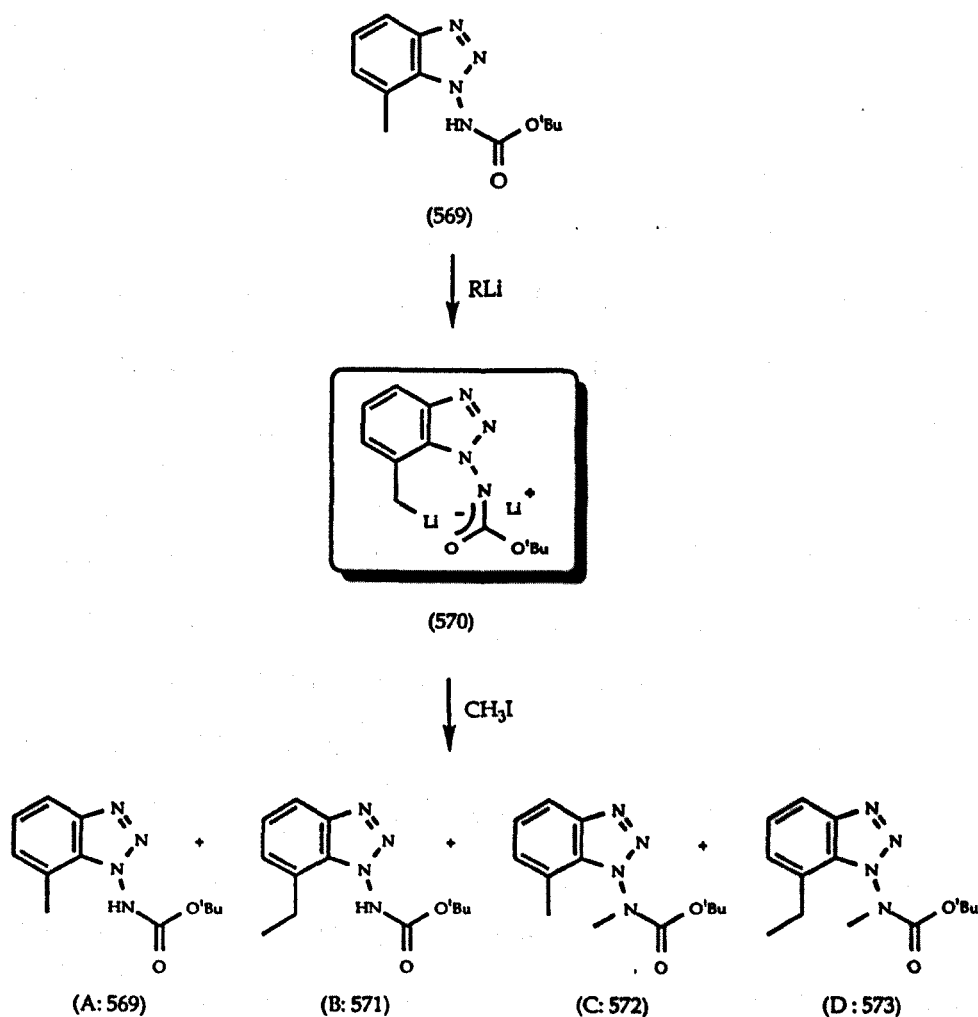
Double protection of primary amines using the BOC group under similar conditions has been previously reported, most notably by Ragnarsson.²²⁸ The fact that double protection of 7-methyl-1-aminobenzotriazole (543) was occurring *in situ* without isolation of the mono adduct suggested to us that double protection was taking place in a

very rapid manner, with the mono adduct possessing a very short lifetime under these reaction conditions.

Studies on determining the optimum conditions required for the metallation of BOC-protected 7-methyl-1-aminobenzotriazole (569) were then undertaken (Scheme 191; Table 7). For our initial studies, the conditions outlined by Clark were applied, where *sec*- or *tert*-butyllithium is used at temperatures in the region of -20°C and -40°C. Additionally, the 'special' electrophile methyl iodide was used in each case, because of its' very high reactivity and lack of competing sites of deprotonation.

The addition of BOC-protected 7-methyl-1-aminobenzotriazole (569) to *sec*-butyllithium at -40°C resulted in the formation of a burgundy red solution, which indicated that some degree of lithiation was taking place (entry 1). After 5 minutes at -40°C, methyl iodide was added to the reaction mixture. Spectroscopic analysis of the isolated crude material indicated, however, that poor alkylation of the starting material had occurred (~ 10%). The same conditions were applied in a repeat reaction, but with the substrate being exposed to the base for a longer period, this time for 0.5h (entry 2); a similarly low level of alkylation (~ 10%) under these conditions was again encountered. Therefore, in an attempt to overcome this poor level of alkylation, a switch to the use of stronger bases at lower temperatures was made. However, using Schlosser's base (potassium *t*-butoxide-activated *n*-butyllithium)²²⁹ at -78°C led to complete failure of alkylation, with total recovery of the starting material ensuing (entry 3). The potential of N, N, N', N'-tetramethylethylenediamine [TMEDA] to act as a base activator was then studied. This amine is one of the most widely used activating agents, and is used in conjunction with either *n*-, *sec*-, or *tert*-butyllithium. Because of its' relative ease of handling compared to the other bases, *n*-butyllithium was chosen as the base in subsequent reactions. Thus, a solution of the aminobenzotriazole (569) and TMEDA-activated *n*-

butyllithium was stirred at -78°C for 0.5h (*entry 4*). A slight improvement in the yield of alkylated product was found ($\sim 15\%$). The reaction was repeated using the same activated base system, but then allowed to warm up to -40°C over 0.5h (*entry 5*). Spectroscopic analysis of the crude material obtained suggested that four inseparable components had been formed, two of which were the starting material and the desired product (571). The other two components were tentatively assigned as the *N*-methylated product (572) and the doubly alkylated product (573), which suggested that at warmer temperatures, competing *N*-alkylation by methyl iodide was posing a serious problem, by interfering with *C*-alkylation.



Scheme 191

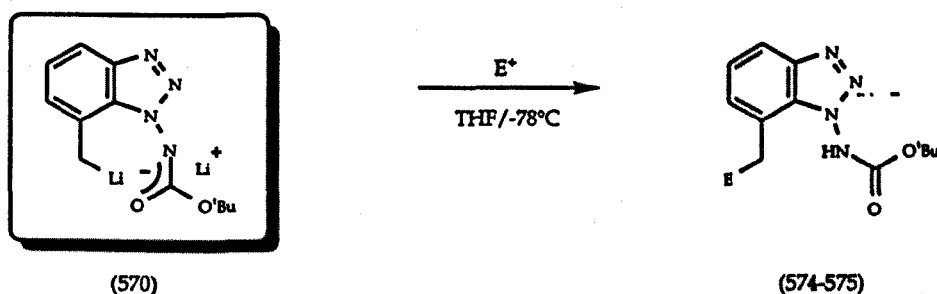
<u>ENTRY</u>	<u>CONDITIONS</u>	<u>RATIO (A:B:C:D)</u>	<u>RECOVERY (%)</u>
1	s-BuLi/-40°C/5 min	~ 90:10:0:0	89
2	s-BuLi/-40°C/0.5h	~ 90:10:0:0	93
3	n-BuLi/KO ^t Bu/-78°C/3h	~ 100:0:0:0	91
4	n-BuLi/TMEDA/-78°C/0.5h	~ 85:15:0:0	89
5	n-BuLi/TMEDA -78°C ~ -40°C/0.5h	~ 1:1:1:1	92
6	n-BuLi/TMEDA -78°C ~ 0°C/0.5h ~ -78°C	~ 0:100:0:0	95

Table 7; Alkylation of the Dianion (570)

Assuming that higher temperatures were required for complete lithiation of the dianion, the conditions employed in *entry* 5 were repeated, with the reaction mixture being left at 0°C for a period of 0.5h (*entry* 6). Also, by assuming that the carbanion would be more reactive than the N-centred species at lower temperatures, the reaction mixture was re-cooled to -78°C prior to addition of the electrophile. Subsequent spectroscopic analysis of the crude material indicated that both alterations were successful in encouraging lithiation, as the desired BOC-protected 7-ethyl-1-aminobenzotriazole (571) was isolated as a colourless gum in 95% yield after chromatography. The reaction was then repeated and allowed to warm above 0°C. ¹H NMR analysis of the crude material provided little evidence for either starting material or product being isolated, and this suggested that above 0°C, the dianion (569) was unstable to organolithium bases.

Although the excellent return of 95% for the adduct (571) indicated that the dianion (569) was being formed in essentially quantitative yield, the

potential to use this species for 1,3-diene incorporation in our IMDA studies still had to be ascertained. To show whether this could be achieved or not, alkylation of the dianion using ethyl iodide as a model electrophile was attempted, as this species would be both less reactive, and prone to competing deprotonation. To our delight, ^1H NMR analysis showed that the crude material obtained was mainly the BOC-protected 7-propyl-1-aminobenzotriazole (574). The excellent 90% yield obtained after chromatography, and the apparent lack of competing deprotonation of the electrophile in this reaction, suggested that the dianion (569) was conforming to the previously mentioned general pattern of sp^3 -centred carbanions being more nucleophilic, and less basic than sp^2 -centred counterparts.^{216, 217} A similarly high yield of 85% was obtained for the BOC-protected 7-butenyl-1-aminobenzotriazole (575) when using allyl bromide as the electrophile.²³⁰

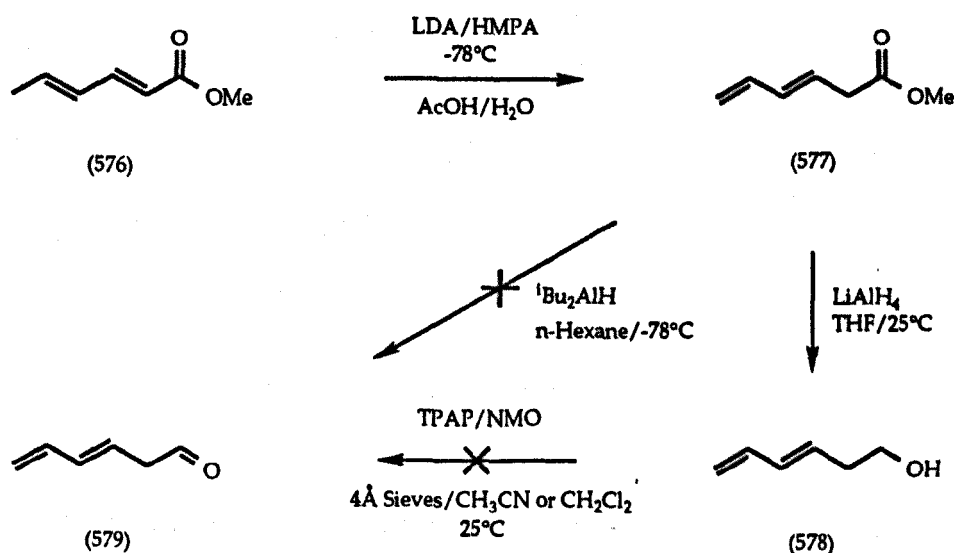


Scheme 192

<u>ELECTROPHILE</u>	<u>PRODUCT</u>	<u>YIELD (%)</u>
$\text{CH}_3\text{CH}_2\text{I}$	(574)	90
$\text{CH}_2=\text{CHCH}_2\text{Br}$	(575)	85

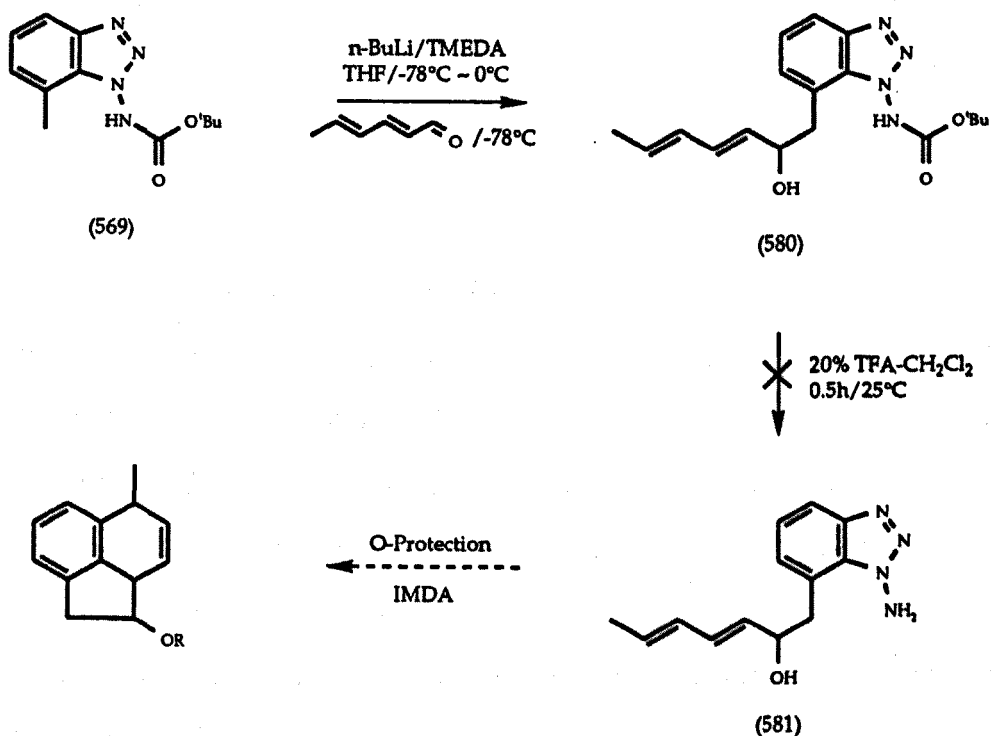
Table 8; Functionalisation of Dianion (570)

Now in a position to attempt 1,3-diene incorporation for IMDA studies, we decided to combine our desire to study such reactions with our interest in determining whether aldehydes could be used to functionalise the dianion (570). Thus, the preparation of 3,5-hexadienal (579) from methyl-2,4-hexadienoate (576) was attempted (*Scheme 193*). Deconjugation of the hexadienoate upon exposure to LDA in THF in the presence of hexamethylphosphoramide [HMPA] at -78°C ²³¹ yielded the 3,5-dienoate (577) after distillation as a pale yellow oil in 58-63% yield. Reduction of this ester using DIBAL-H in *n*-hexane at -78°C gave a complex, inseparable mixture of materials, spectroscopic analysis of which failed to give any evidence of formation of the aldehyde (579). Synthesis of the aldehyde was then attempted in a more conventional two step process. Reduction of the methyl ester (577) using lithium aluminium hydride in THF²³² yielded the alcohol (578) as a white amorphous solid in 90-95% yield. However, oxidation of the alcohol using catalytic tetra-*n*-propylammonium perruthenate [TPAP]²³³ at ambient temperature again failed to yield the desired aldehyde, with an inseparable mixture of materials being isolated instead.



Scheme 193

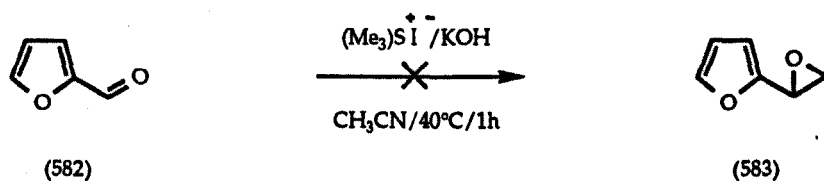
Failure to synthesize 3,5-hexadienal (579) forced us to consider other suitable 1,3-dienes required for incorporation. Instead of trying to make unstable aldehydes for use as electrophiles, we decided to use commercially available 2,4-hexadienal. Thus, addition of the aldehyde to a solution of the dianion (570) at -78°C yielded the adduct (580) as a yellow-green glass in a poor yield of 37%. Rather unsurprisingly, when attempting to remove the BOC group under standard deprotection conditions using excess trifluoroacetic acid [TFA] in dichloromethane at ambient temperature,²²⁷ dehydration of the sensitive secondary alcohol occurred, resulting in the decomposition of the starting material, with none of the desired product (581) being isolated (Scheme 194).



Scheme 194

One final attempt at incorporating a 1,3-diene moiety was aimed at attempting an IMDA reaction with an attached furanyl moiety, as these

cyclic 1,3-dienes tend to undergo Diels-Alder reactions in a very efficient manner. Keeping in line with our investigations into which electrophiles were suitable for functionalising the dianion (570), incorporation of the furan ring was envisaged using a furyl epoxide such as 2-furyloxirane (583), thus testing the ability of the dianion to react with epoxides. The synthesis of furyl-2-oxirane from 2-furaldehyde (582) was reported by a French group,²²⁸ and attempts to repeat this were made (*Scheme 195*). Unfortunately, treatment of the furaldehyde with one equivalent of trimethylsulphonium iodide in the presence of potassium hydroxide using acetonitrile as the solvent at 40°C failed to yield any of the desired epoxide.



Scheme 195

The severe difficulties that were being encountered whilst attempting to prepare suitable 1,3-dienes for the key IMDA processes brought to our attention the fact that similar problems would have to be tackled for every single 1,3-diene electrophile which would be required. As this was going to require a lot of effort and concentration in the process, it was felt that the synthesis of such suitable species would overshadow the subsequent cycloaddition reactions that were to be attempted. Consequently, studies on the IMDA reactions of benzyne were curtailed.

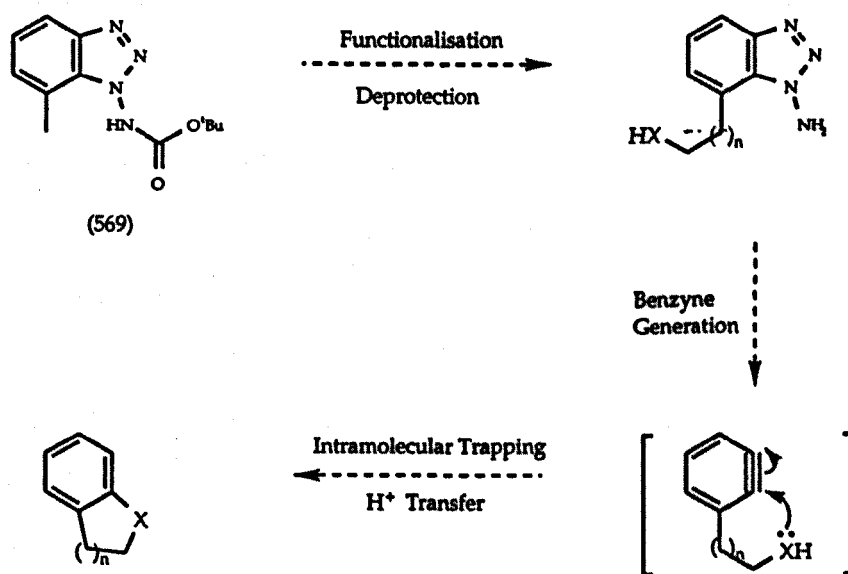
CHAPTER SIX

Intramolecular Trapping of Benzyne By Hydroxyl Groups: A Novel Approach to Dihydrobenzofurans and Chromans

- a) Introduction*
- b) Approaches to Benzofurans and Dihydrobenzofurans*
- c) Approaches to Chromans*
- d) A Novel Intramolecular Benzyne Cyclisation Approach To Dihydrobenzofurans and Chromans*
- e) Summary*
- f) Future Work*

a) Introduction

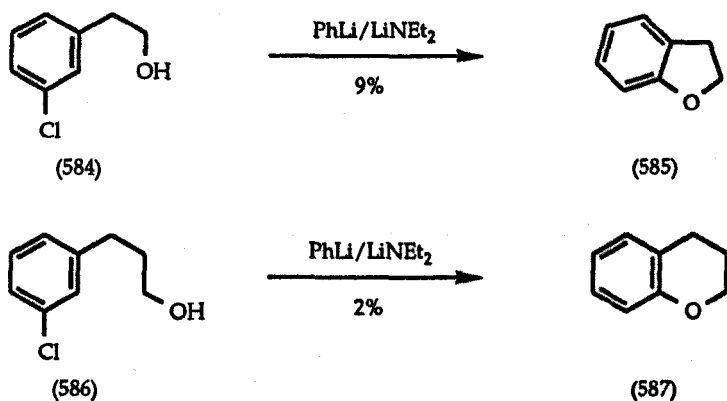
As outlined in Chapter Three, one of the major applications of benzyne in organic synthesis is the construction of benzo-fused heterocycles *via* the intramolecular trapping by flanking nucleophiles. Taking this into account, failure to construct suitable *ortho*-substituted 1-aminobenzotriazoles for IMDA reactions, as reported in Chapter Five, led us to take a look at constructing similar species for intramolecular benzyne cyclisations, with incorporation of the nucleophile (X) being accomplished *via* the functionalisation of BOC-protected 7-methyl-1-aminobenzotriazoles (569) (Scheme 196). To our knowledge, no previous examples of intramolecular benzyne trapping using *ortho*-substituted 1-aminobenzotriazole derivatives had been previously reported.



Scheme 196

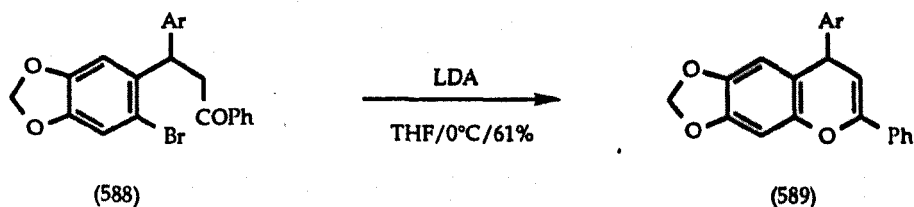
Of particular interest to us was the synthesis of benzofused oxygen heterocycles, in particular dihydrobenzofurans ($n = 1$) and chromans ($n = 2$),

which could be effected *via* the trapping of benzyne by hydroxyl functions ($X = O$); this choice was based upon the lack of reported syntheses of these ring systems *via* benzyne-mediated processes. The oldest example was due to Huisgen,^{76b} who reported the synthesis of the parent dihydrobenzofuran (585) and chroman (587) species *via* the trapping of the benzyne by a flanking primary alcohol function in poor yields, reflecting the poor nucleophilicity of the oxyanion compared to the base used (*Scheme 197*).



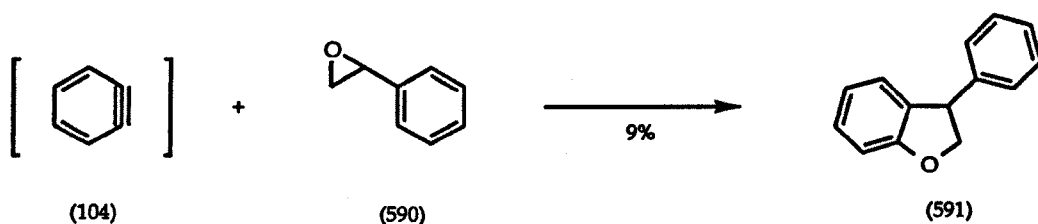
Scheme 197

Two groups of examples of benzo-fused oxygen heterocyclic syntheses were reported more recently. Castedo *et al*¹⁶⁸ reported the trapping of benzyne by flanking phenoxide anions in the synthesis of Cularine alkaloids in low yields (see *Scheme 125*), whilst Jung and Lowen reported the synthesis of 4H-chromenes (589) *via* the intramolecular trapping of a benzyne by a flanking enolic OH moiety (*Scheme 198*).⁶⁴



Scheme 198

An intermolecular benzyne approach to 3-phenyldihydrobenzofuran (591) was reported by Stiles, with heterocyclic synthesis being effected in poor yield *via* the addition of styrene oxide (590) to *ortho*-benzyne (104) (Scheme 199).³⁶ⁱ



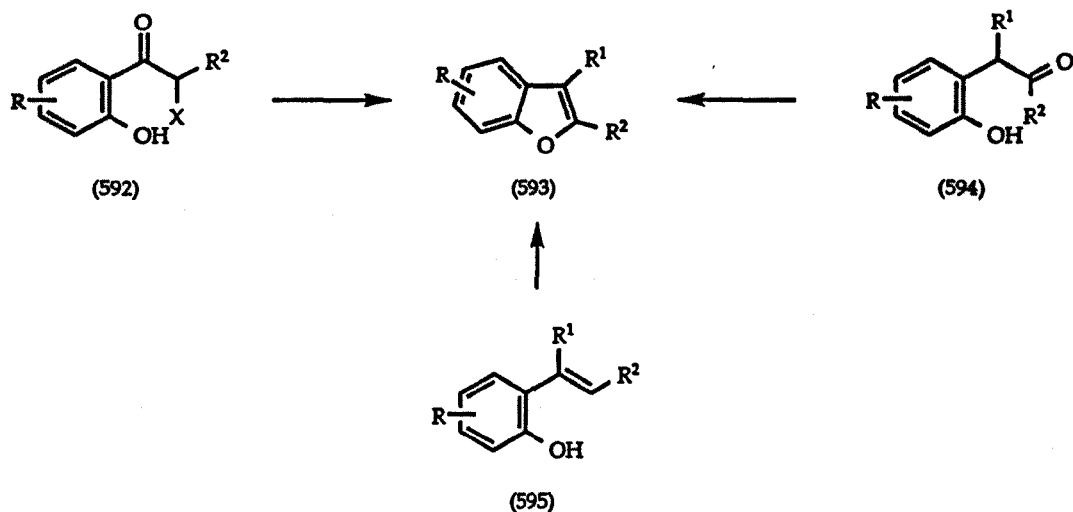
Scheme 199

b) Approaches to Benzofurans and Dihydrobenzofurans

Since its discovery around 100 years ago, the benzofuran ring system has been the focus of much research, with the interest in this heterocyclic system stemming from the number of naturally occurring and physiologically active compounds which incorporate this structure. Numerous synthetic approaches to the benzofuran ring system have been reported and compiled in various reviews, and the reader is asked to survey these reviews for a more in-depth study.²³⁵

Ring Closure of ortho-Substituted Phenols

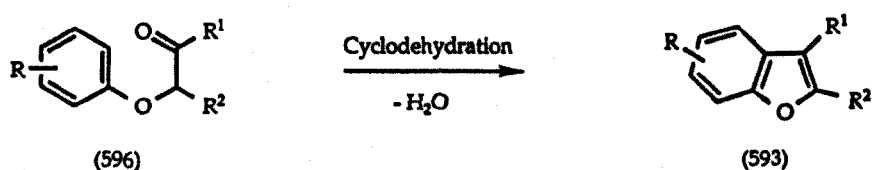
The nucleophilic attack of a phenol onto *ortho*-substituents is one of the most common routes to the benzofurans (593). Some of the substituents which have been used include halogenated ketones (592, X = halogen), benzylic aldehydes or ketones (594, R² = H, alkyl), or unsaturated alkyl chains (595, R¹ = H, alkyl, aryl, R² = H, alkyl) (Scheme 200).



Scheme 200

Cyclodehydration of Aryloxy- α -carbonyl Species

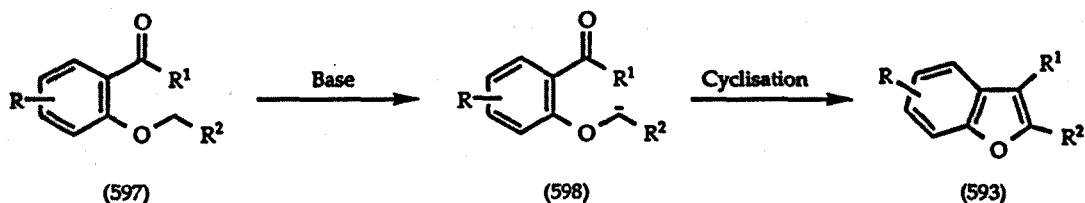
Benzofuran synthesis is also possible *via* the dehydration of α -aryloxycarbonyl species (596) such as aldehydes ($\text{R}^1 = \text{H}$), ketones ($\text{R}^1 = \text{alkyl, aryl}$) or carboxylic acids ($\text{R}^1 = \text{OH}$), with phosphorus oxychloride and sulphuric acid used as the most common dehydrating agents (*Scheme 201*).



Scheme 201

Ring Closure of α -Aryloxyalkanoic Acids

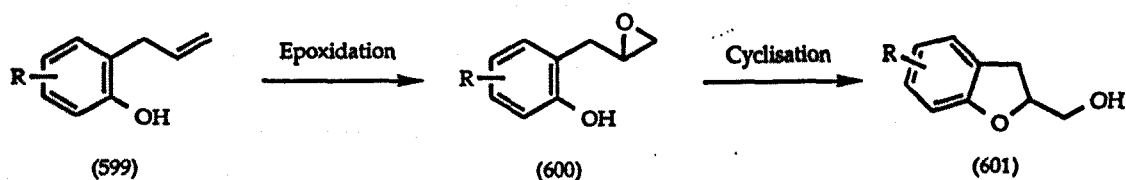
This other common route to benzofurans concerns the intramolecular aldol condensation of α -*ortho*-acylaryloxyalkanoic acids (597, $\text{R}^2 = \text{COOH}$) or esters ($\text{R}^2 = \text{COOR}$) (*Scheme 202*).



Scheme 202

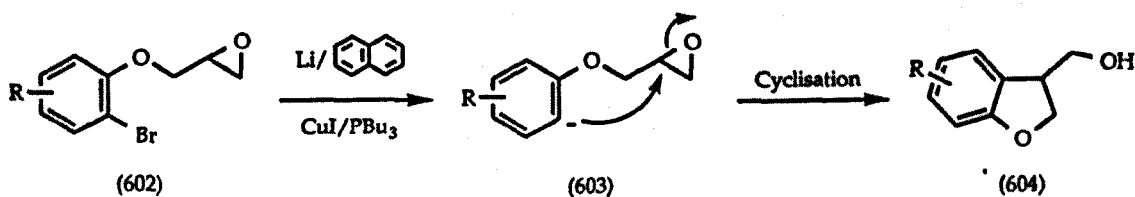
Recent Approaches to Dihydrobenzofurans

Numerous specialised routes to dihydrobenzofurans have been reported. Amongst these is the intramolecular nucleophilic attack of phenols onto *ortho*-substituted epoxides (600) (Scheme 203).³⁶ⁱ



Scheme 203

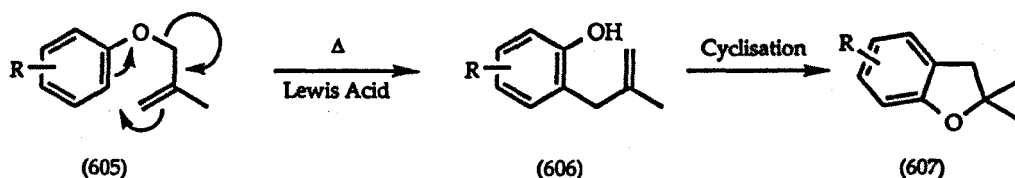
Riecke *et al* have recently reported an intramolecular epoxide ring opening process leading to the synthesis of 3-substituted dihydrobenzofurans (604), where the reaction of epoxy aryl halides (602) is mediated by phosphine-based active copper species (Scheme 204).²³⁶



Scheme 204

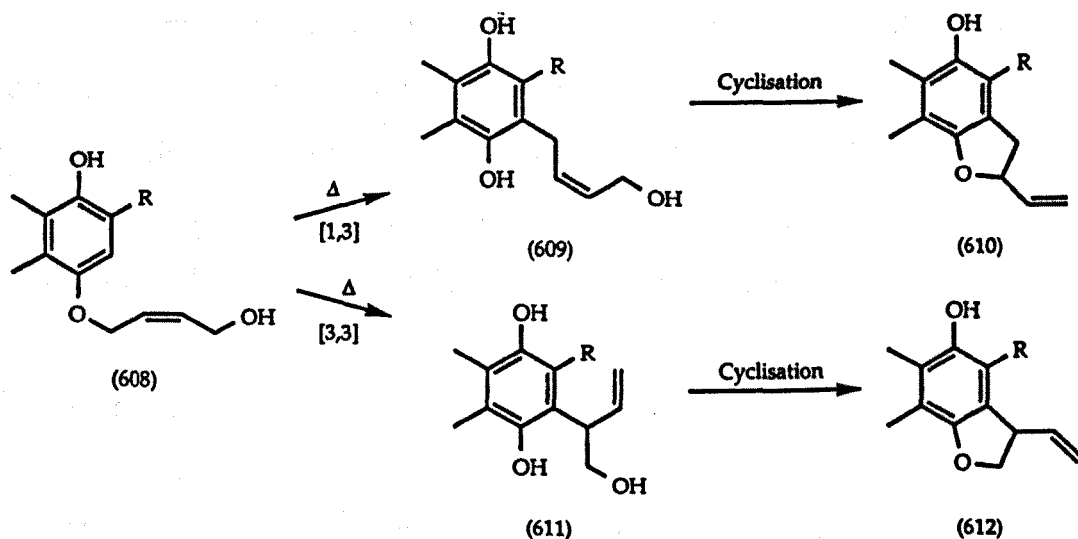
Other recent examples of dihydrobenzofuran syntheses have been

reported where the key synthetic step involves a thermally-induced rearrangement; for example, the one-pot synthesis of 2,2-dimethylbenzofuran derivatives (607) *via* a Lewis-acid catalysed tandem Claisen rearrangement-cyclisation of aryl allyl ethers (605) (Scheme 205).²³⁷



Scheme 205

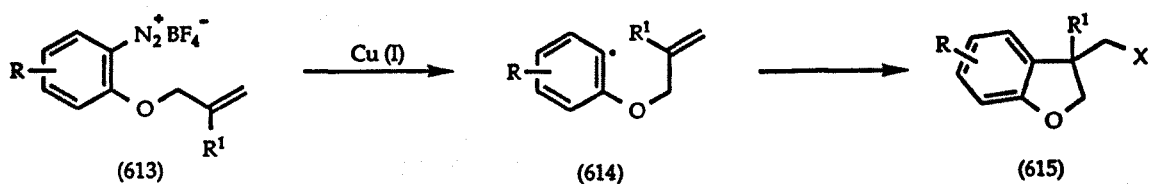
The one-pot synthesis of vinyl-2,3-dihydrobenzofurans has also been reported, where 2-vinyldihydrobenzofurans (610) are formed by a tandem [1,3]-sigmatropic rearrangement-cyclisation of aryl allyl ethers (608), and 3-vinyldihydrobenzofurans (612) are formed *via* a similar process but with a Claisen rearrangement occurring instead (Scheme 206).²³⁸



Scheme 206

An aryl radical-mediated approach to functionalised

dihydrobenzofurans (615, X = halogen, CN, SR) has been reported by Beckwith,²³⁹ where elimination of molecular nitrogen from the diazonium species (613) upon exposure to copper reagents generates an aryl radical intermediate (614), which traps the adjacent *ortho*-substituted aryl allyl ether to give the dihydrobenzofuran (Scheme 207). Murphy has recently developed this route by using tetrathiofulvalene [TTF] as a radical-polar crossover reagent which mediates the cyclisation process.²⁴⁰



Scheme 207

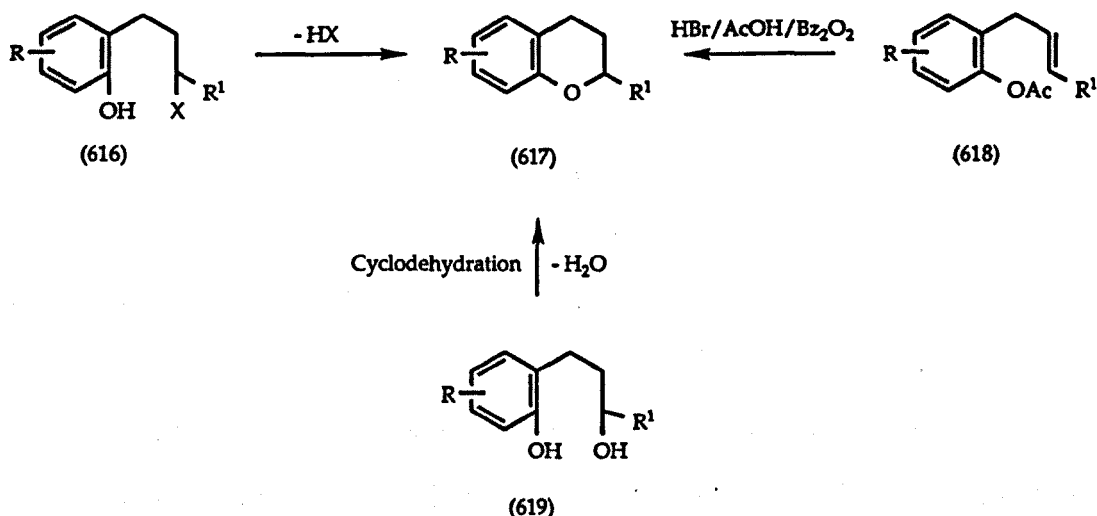
c) Approaches to Chromans

The family of chromans [1H-benzopyrans] have been given a substantial amount of attention ever since the discovery that the naturally occurring family of Tocopherols (including Vitamin E) possessed this particular ring system.²⁴¹ A number of general methods of preparation have been applied to the synthesis of chroman and its derivatives, and the more important and general methods have been outlined below.

From ortho-Substituted Phenols

The cyclisation of 1-(2-hydroxyphenyl)propane derivatives (616) *via* the nucleophilic displacement of a leaving group (X = halogen) by a phenol group is one of the oldest and most widely used routes to chromans (617), with the preparation of the parent chroman using this route being reported

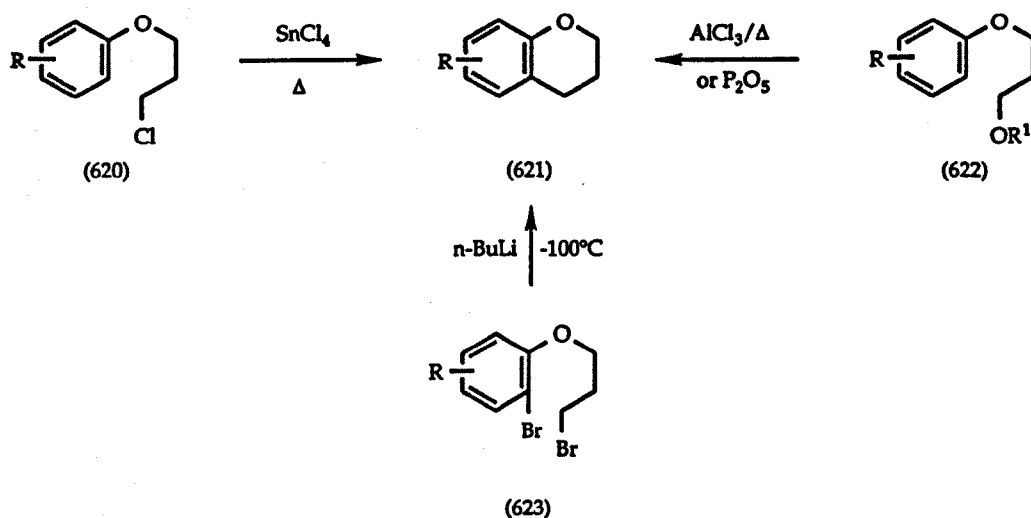
in 1905. Synthesis of chromans has also been reported *via* the ring closure of phenol acetates (618), which can be accomplished using hydrogen bromide-acetic acid in the presence of benzoyl peroxide [Bz₂O₂]. Another route to chromans which has been extensively used involves the dehydration of 3-(dihydroxyphenyl)propan-1-ols (619) upon exposure to phosphorus pentoxide or sulphuric acid (*Scheme 208*).



Scheme 208

From Arylalkoxy Ethers

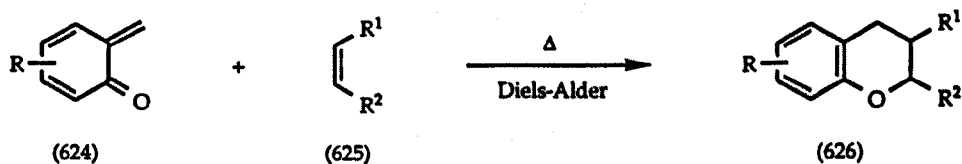
A number of widely used chroman syntheses are based on the cyclisation of phenoxypropane derivatives. Under Friedel-Craft conditions, the cyclisation of 1-chloro-3-phenoxypropane derivatives (620) can be effected using tin(IV) chloride. A similar cyclisation can also be effected by the use of aluminium trichloride on 1-alkoxy-3-phenoxypropanes (622, R¹ = alkyl, aryl), whilst 1-hydroxy-3-phenoxypropanes (R¹ = H) also yield chromans upon reaction with phosphorus pentoxide. Chromans can also be generated *via* the action of *n*-butyllithium on 1-bromo-3-(2-bromophenoxy)propane derivatives (623) (*Scheme 209*).



Scheme 209

Via Diels-Alder Cycloadditions

The synthesis of chromans (626) *via* Diels-Alder reactions has also been reported, for example between *ortho*-quinonemethides (624) and a suitable dienophile (625, $\text{R}^1, \text{R}^2 = \text{alkyl, aryl}$) (Scheme 210).

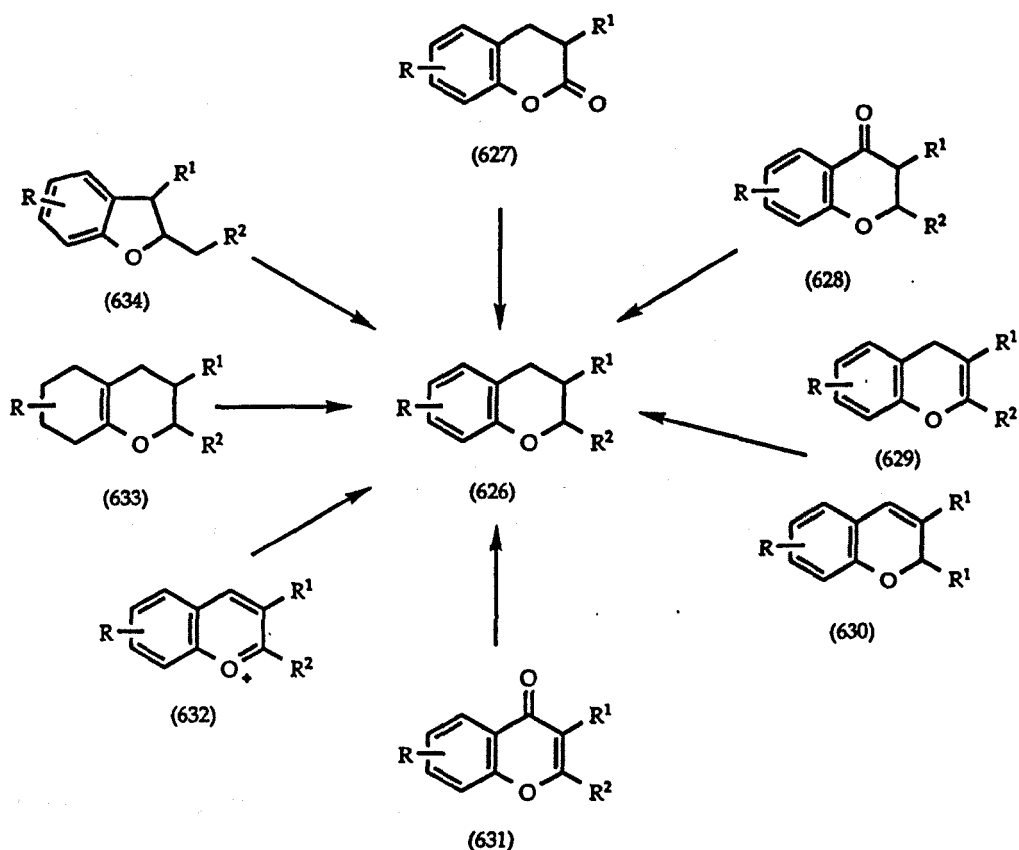


Scheme 210

From Chroman Derivatives

Numerous syntheses of chromans (626) *via* the functional group manipulation of related heterocycles have been reported. These include the conversion of coumarins (627) *via* exposure to Grignard reagents, from chromanones (628) *via* either catalytic hydrogenolysis or Clemmenson

reduction, the catalytic hydrogenation of 2H- and 4H-chromenes (629 and 630), reduction of chromones (631) and benzopyrillium salts (632), and *via* the oxidation of annulated pyrans (633). The isomerisation of dihydrobenzofurans into chromans has also been utilised (634).



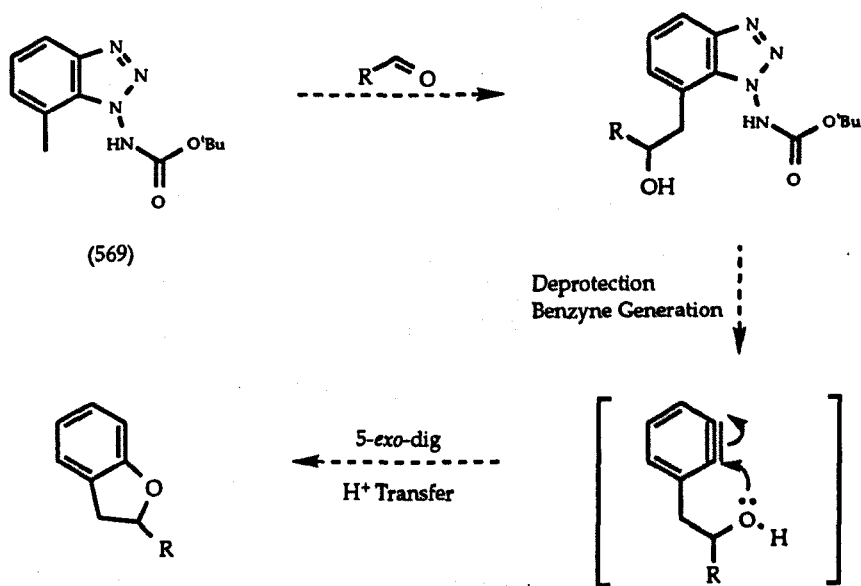
Scheme 211

d) A Novel Intramolecular Benzyne Cyclisation Approach to Dihydrobenzofurans and Chromans

Dihydrobenzofuran Synthesis

The condensation of BOC-protected 7-methyl-1-aminobenzotriazole (569) with aldehydes appeared to be a suitable route to 2-substituted dihydrobenzofurans, with the hydroxyl function required for intramolecular

trapping being generated during the functionalisation step. Removal of the BOC group, followed by exposure of the *ortho*-substituted benzyne precursor to suitable reagents would result in intramolecular cyclisation proceeding *via* a 5-*exo*-dig process (Scheme 212).²⁴²



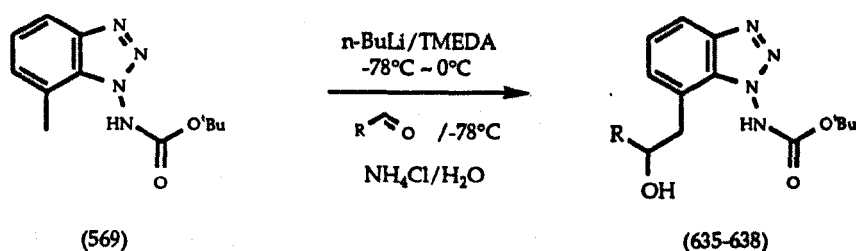
Scheme 212

Although BOC-protected 7-methyl-1-aminobenzotriazole (569) had been previously homologated with 2,4-hexadienal in a preliminary study (see Chapter Five), the potential for incorporating aldehydes had to be properly ascertained, and so a series of condensations using various model aldehydes was undertaken. Here, problems associated with *N*-alkylation, which were encountered when using alkyl halides, would clearly be avoided as resulting hemiaminals would be too unstable to isolate.

Using non-enolisable aldehydes, alkylation appeared to proceed in a satisfactory manner, though not as efficiently as for alkyl halides. Condensation of the dianion derived from the aminobenzotriazole (569) with benzaldehyde yielded the corresponding secondary alcohol (635) as a

colourless gum in 85% yield after chromatography, whilst a similar yield of 81% was obtained for the adduct (636) when using 2-furaldehyde.

A more rigorous test for functionalising with aldehydes was conducted when using enolisable aldehydes as electrophiles, where competing deprotonation of the aldehyde could interfere with condensation. The addition of *n*-hexanal to the dianion derived from (569) resulted in a slower dissipation of the colour of the solution, and following stirring at -78°C for 3h, spectroscopic analysis of the crude material confirmed the formation of the product (637), which was isolated as a colourless gum in an unoptimised 55% yield after chromatography. A similar result was obtained when citral was used, with the adduct (638) being obtained as a colourless gum in an unoptimised yield of 53%.²³⁰

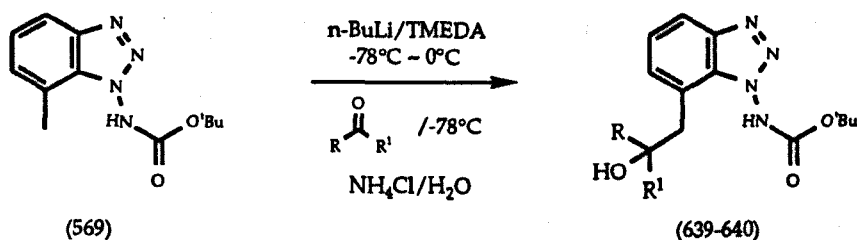


Scheme 213

<u>ELECTROPHILE</u>	<u>PRODUCT</u>	<u>YIELD (%)</u>
C ₆ H ₅ CHO	(635)	85
2-Furyl-CHO	(636)	81
CH ₃ (CH ₂) ₄ CHO	(637)	55
(±)-Citral	(638)	53

Table 9; Functionalisation of (569) with Aldehydes

The preparation of 2,2-disubstituted dihydrobenzofurans appeared to be possible by the condensation of the aminobenzotriazole (569) with ketones in a similar manner to aldehydes, where competing *N*-alkylation would again be kept to a minimum. Using acetone as a model electrophile, the tertiary alcohol (639) was obtained after chromatography as an amorphous, white powder in an unoptimised 70% yield. Similarly, condensation of (569) with cyclohexanone yielded the corresponding alcohol (640) as an amorphous, white powder in an unoptimised yield of 62% after chromatography.²³⁰



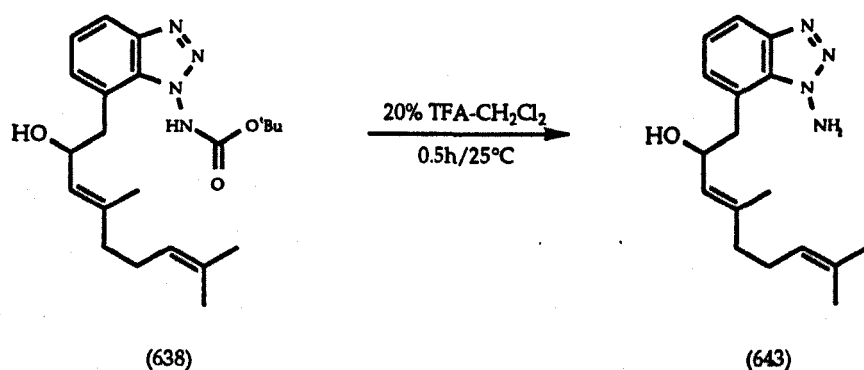
Scheme 214

<u>ELECTROPHILE</u>	<u>PRODUCT</u>	<u>YIELD (%)</u>
(CH ₃) ₂ CO	(639)	70
C ₆ H ₁₀ O	(640)	62

Table 10; Functionalisation of (569) with Ketones

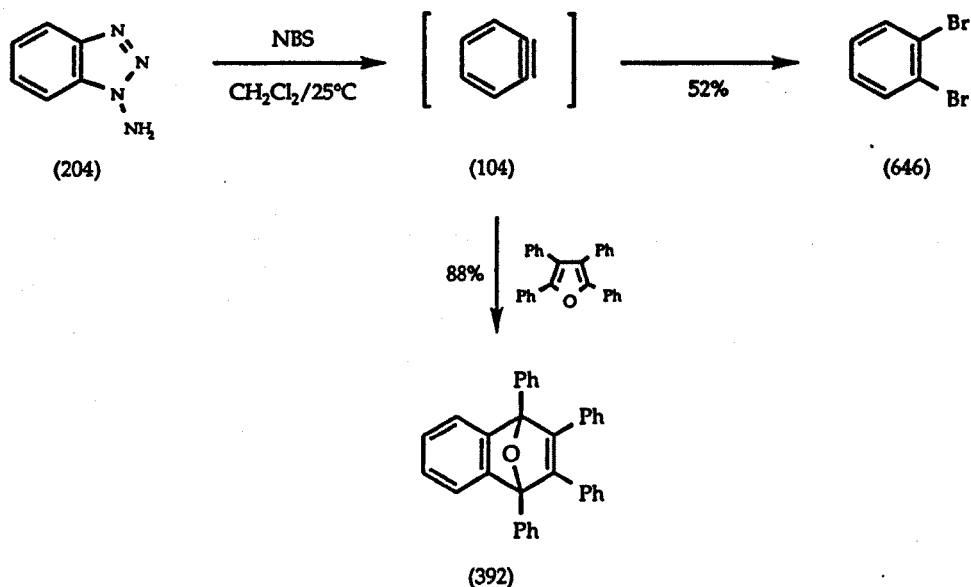
Removal of the BOC group from a selection of the alcohols was attempted using TFA at ambient temperature (*Scheme 215; Table 11*).²²⁷ For the benzaldehyde adduct (635), the susceptibility of the secondary alcohol to undergo acid-catalysed dehydration was highlighted by the moderate yield of 45% which was obtained for the deprotected 1-aminobenzotriazole (641).

The extremely sensitive nature of the secondary alcohol in the citryl adduct (638) rather unsurprisingly resulted in failure, with none of the deprotected 1-aminobenzotriazole (643) being isolated. Assuming that *in situ* generated t-butyl cations were inducing dehydration of the secondary alcohol,²⁴³ deprotection was repeated in the presence of t-butyl scavengers. The poor scavenging ability of t-butyl cations by anisole²⁴⁴ was confirmed by its failure to alleviate the problem of decomposition. The use of thiophenol²⁴⁵ did lead to a certain improvement, with the substituted 1-aminobenzotriazole being isolated as a pale brown gum in a moderate 52% yield after chromatography.



Scheme 216

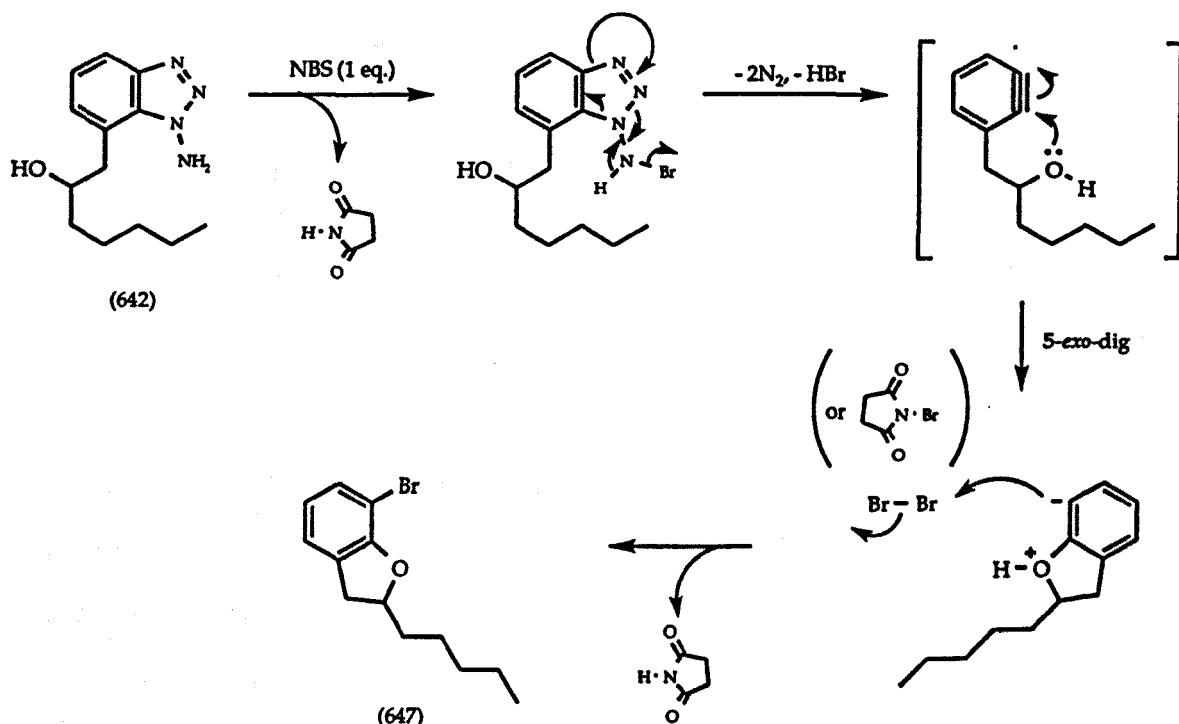
Although according to the literature lead(IV) acetate is considered to be the standard reagent for benzyne generation from 1-aminobenzotriazoles, other oxidising agents can be used to induce benzyne formation, most notably N-bromosuccinimide [NBS], which appears to generate *ortho*-benzyne (104) in a comparable manner; for the addition of 1-aminobenzotriazole to NBS without a trap, Rees reported that 1,2-dibromobenzene (646) was isolated in 52% yield, formed probably *via* bromine scavenging, whilst with tetraphenylfuran, the resulting cycloadduct (392) was obtained in an excellent yield of 88% (Scheme 217).²⁴⁶



Scheme 217

With benzyne generation using NBS appearing to be more favourable than using lead(IV) acetate because of the milder conditions, initial attempts at benzyne generation from the substituted 1-aminobenzotriazoles (641-642, 644-645) were made using the former reagent. The addition of the n -hexanal adduct (642) to a solution of two equivalents of NBS in dichloromethane at ambient temperature led to instantaneous effervescence, presumably through the evolution of nitrogen, and the development of an orange solution, presumably as a result of bromine formation. Tlc and spectroscopic analysis of the crude material showed the formation of several components. Careful separation of these by column chromatography yielded a compound which appeared to be a dihydrobenzofuran. The aromatic region of the ^1H NMR spectrum of this compound, however, did not appear to conform to that of a simple dihydrobenzofuran, and this was later confirmed by High Resolution Mass Spectrometry, which indicated the incorporation of a bromine atom into the product. Further examination of the ^1H NMR spectrum appeared to confirm bromine incorporation, leading to the

structural assignment of the 2-pentyl-7-bromo-dihydrobenzofuran (647) for this product, which was isolated as a colourless oil in 45% yield.

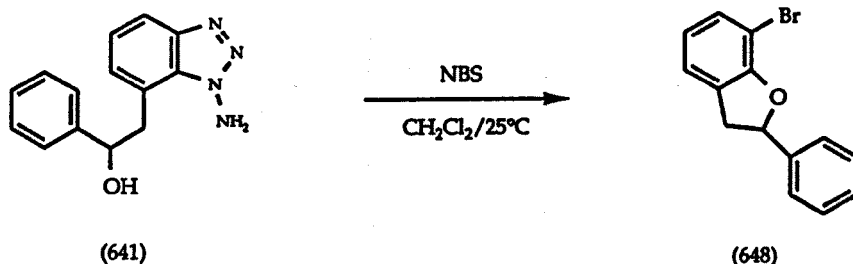


Scheme 218

The formation of the bromo-dihydrobenzofuran (647) was rationalised by the initial generation of the benzyne, followed by the formation of the dihydrobenzofuran, and the trapping of a bromonium species by the aryl anion (Scheme 218). Although the scheme indicates that bromine (generated by the reaction of hydrobromic acid with the second equivalent of NBS) is the bromonium ion source, it is perfectly feasible that the second equivalent of NBS could function directly in this manner.

In a similar manner to the *n*-hexanal adduct, reaction of the benzaldehyde adduct (641) with NBS led to the formation of a crude material which contained several components. Mass spectral data of the compound appearing to contain a dihydrobenzofuran again confirmed bromine incorporation, with the 2-phenyl-7-bromo-dihydrobenzofuran (648)

structure being consistent with all spectroscopic data. The compound was isolated as a colourless oil in another modest yield of 38% (Scheme 219).

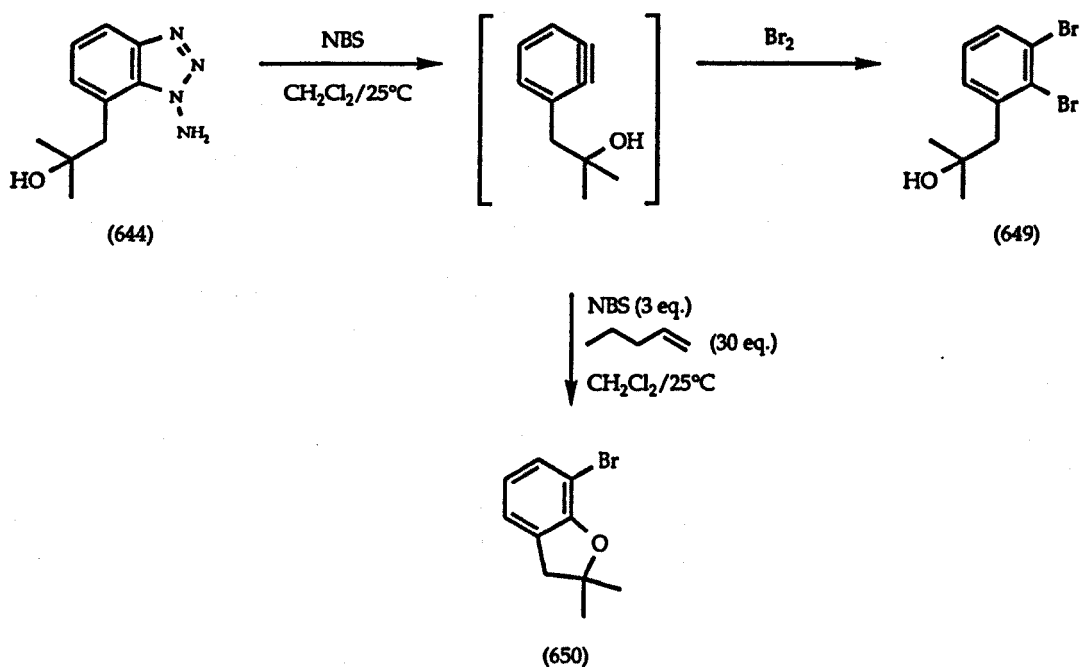


Scheme 219

A more stringent test of intramolecular benzyne cyclisation came when attempting to trap benzynes using the more hindered hydroxyl group of the tertiary alcohols (644) and (645), derived from the acetone and cyclohexanone adducts respectively. The addition of the acetone adduct (644) to NBS in dichloromethane at ambient temperature again led to the formation of a number of components, and careful separation of the crude material yielded what appeared to be from spectroscopic analysis to be the corresponding bromo-dihydrobenzofuran (650), with a characteristic aromatic pattern, and an apparently characteristic CH_2 singlet ($\delta \sim 3.0$ ppm); a ^{13}C NMR spectrum also appeared to confirm this structure, but High Resolution Mass Spectrometry failed to show any sign of ions corresponding to the ring system, and instead indicated that the incorporation of two bromine atoms had occurred, leading to formulation of the product as the 1,2-dibromo species (649), isolated as a colourless oil in 52% yield.

The isolation of the 1,2-dibromo-3-substituted benzene (649) suggested that trapping of the benzyne by the *in situ* generated bromine was occurring at a faster rate than trapping by the flanking hydroxyl group, probably as a result of the more hindered nature of the tertiary alcohol. Further

inspection of the ^1H and ^{13}C NMR data showed that these fitted well for both a dihydrobenzofuran and a 1,2-dibromo-3-substituted benzene, resulting in the initial confusion concerning their assignment.

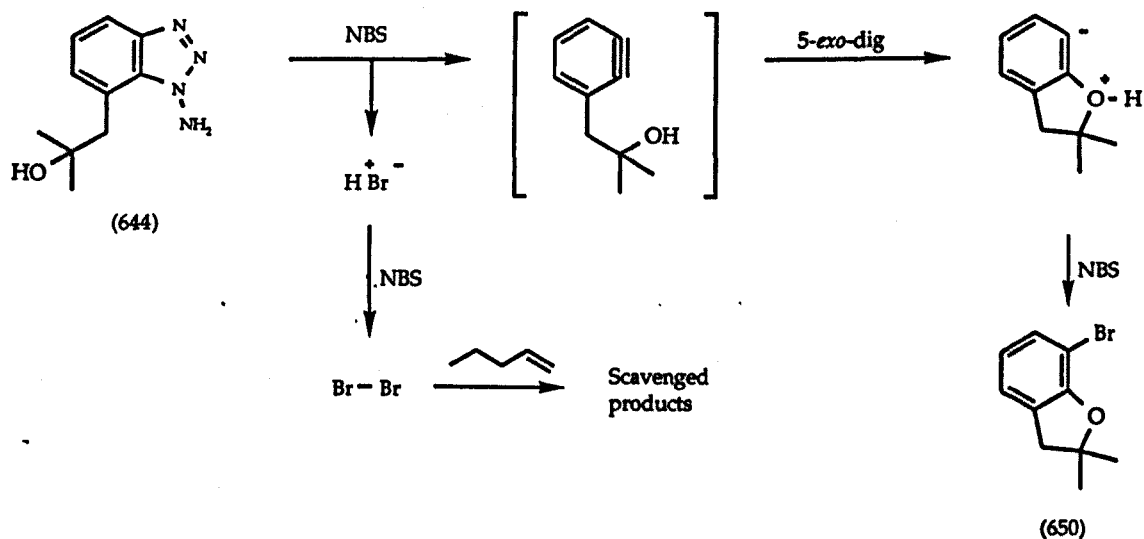


Scheme 220

Working on the assumption that bromine trapping was indeed interfering with dihydrobenzofuran generation, it appeared possible that the addition of a scavenger could result in immediate removal of bromine, and therefore would allow intramolecular trapping to occur. Thus, the reaction of the acetone adduct (644) with NBS was repeated in the presence of a large excess of 1-pentene. Tlc analysis after stirring for 1h showed that starting material was still present in the reaction mixture, and so a further equivalent of NBS was added. This process was repeated twice further until starting material was completely removed, with five equivalents of NBS being required for the overall process. A ^1H NMR spectrum of the component presumed to be the dihydrobenzofuran was similar to that of the 1,2-dibromo species obtained previously, but the aromatic region took the

appearance of those found in the 2-pentyl and 2-phenyl-7-bromo-dihydrobenzofurans (647) and (648). The incorporation of one bromine atom was confirmed by mass spectral data, with the product (650) isolated after chromatography as a colourless oil in a modest yield of 45%.

The requirement of further equivalents of NBS was rationalised on the basis that as bromine was being removed from the reaction mixture by 1-pentene, then to drive the reaction to completion further equivalents of NBS were required to provide the major source of bromonium ions for the bromination of the aryl anion (*Scheme 221*).



Scheme 221

Having shown that the acetone adduct (644) could indeed be cyclised in the presence of 1-pentene, similar attempts to cyclise the cyclohexanone adduct (645) under the same conditions yielded a crude material containing several components. Separation of the crude material yielded a major compound which was not the desired spiro-bromo-dihydrobenzofuran, but unfortunately was shown by High Resolution Mass Spectrometry to be the 1,2-dibromobenzene (651), isolated as a colourless oil in 51% yield (*Scheme 222*).

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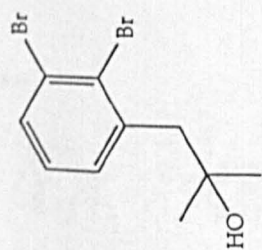
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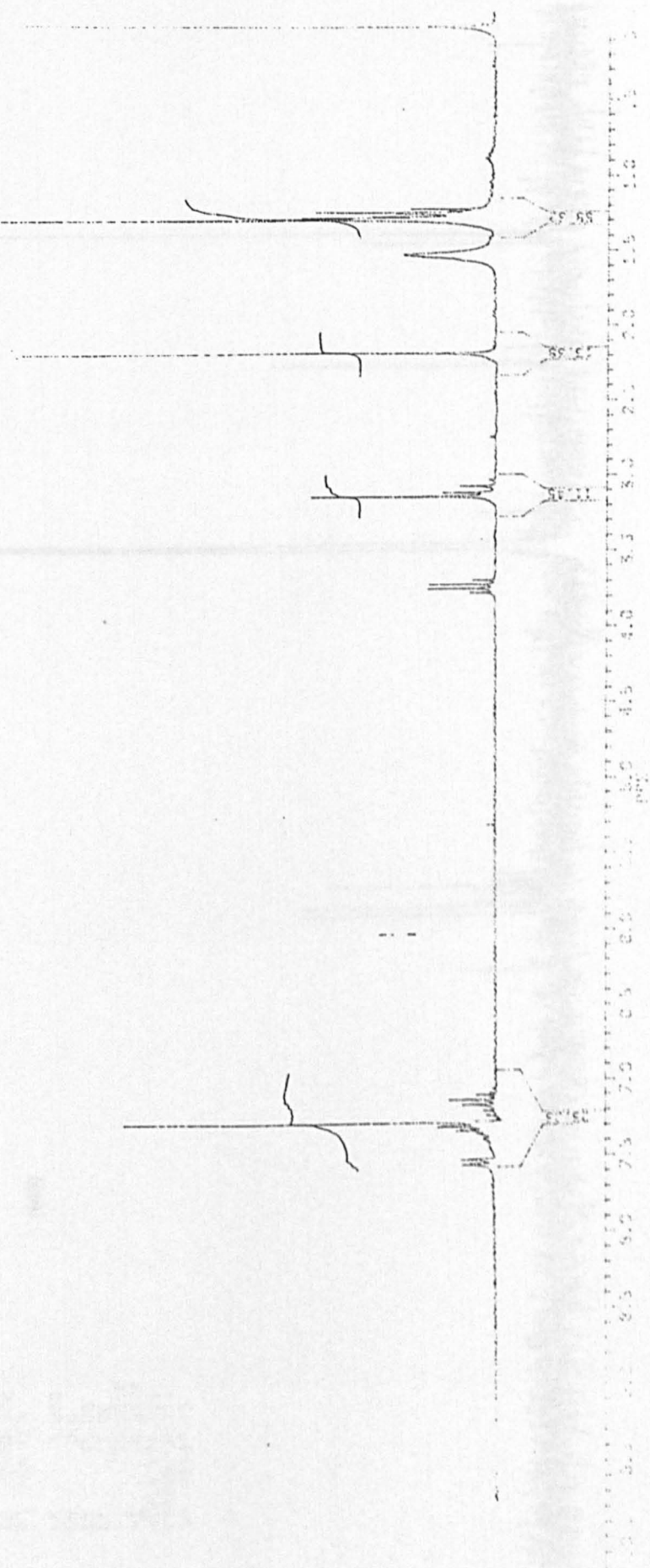


Figure 1a

24

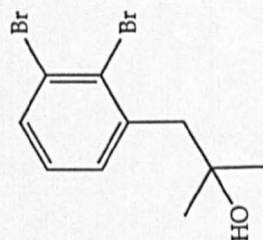
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(649)

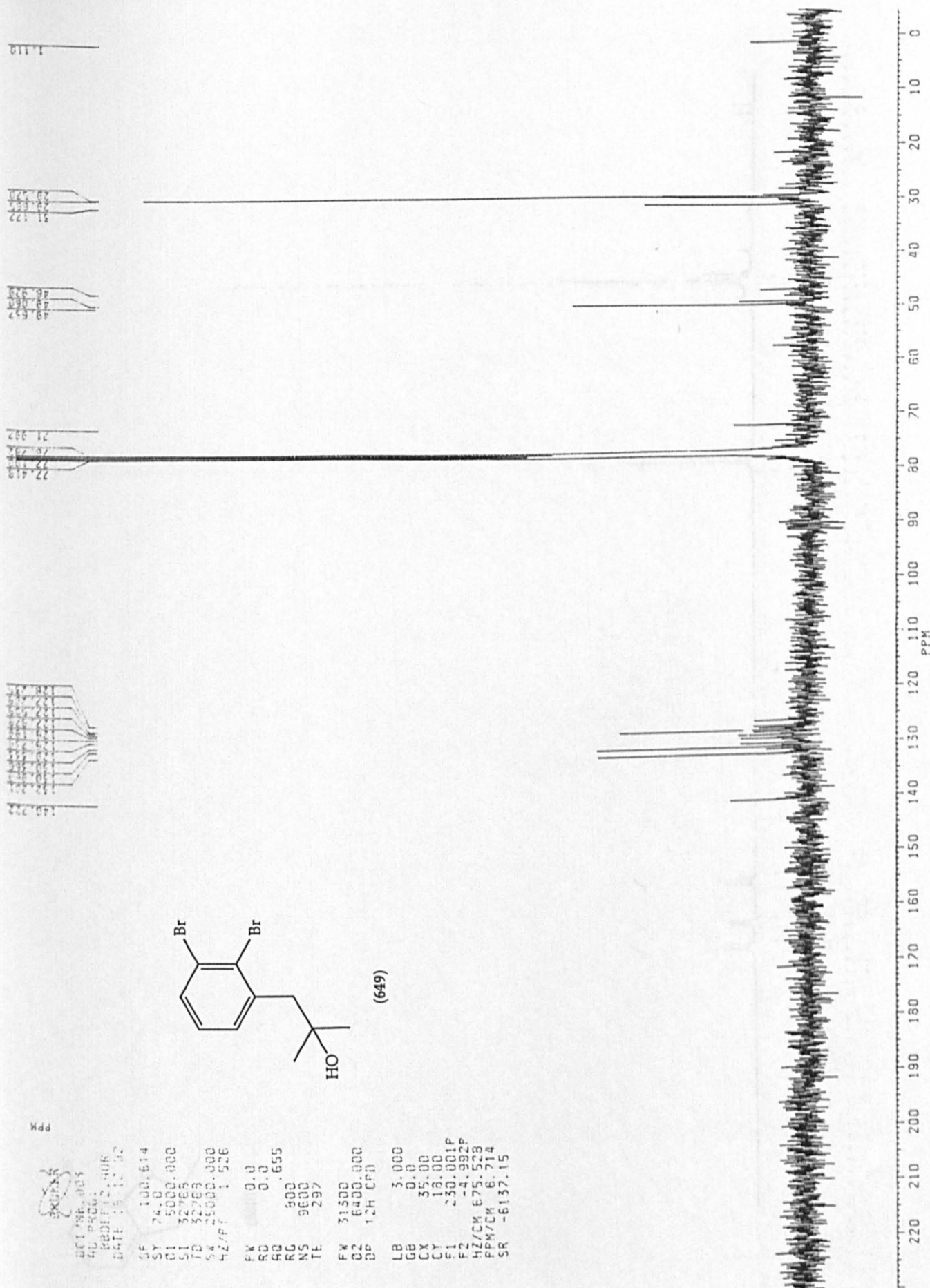
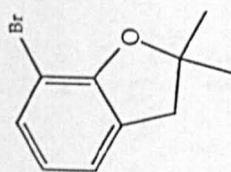


Figure 1b



(650)

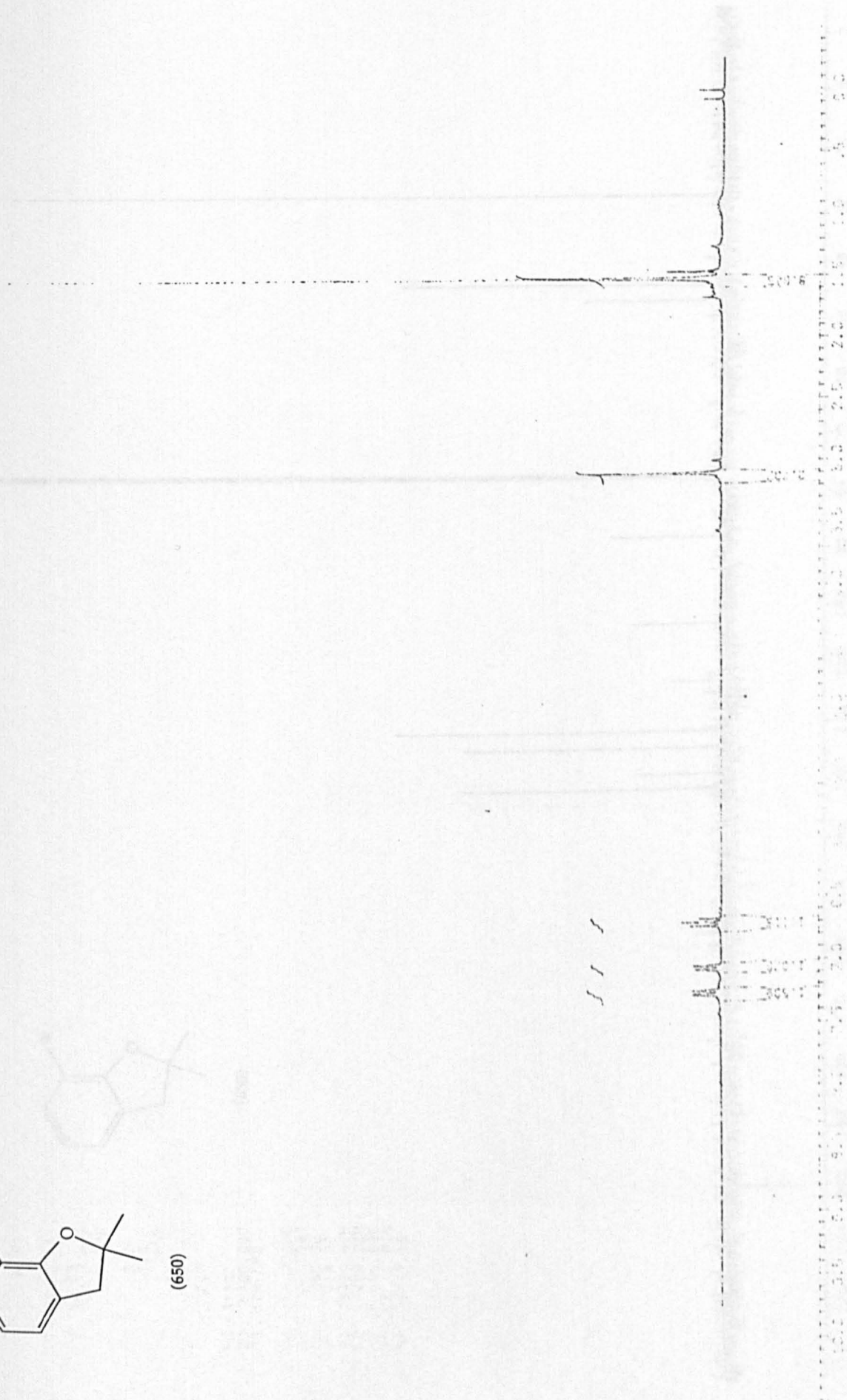
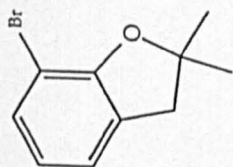


Figure 2a



(650)

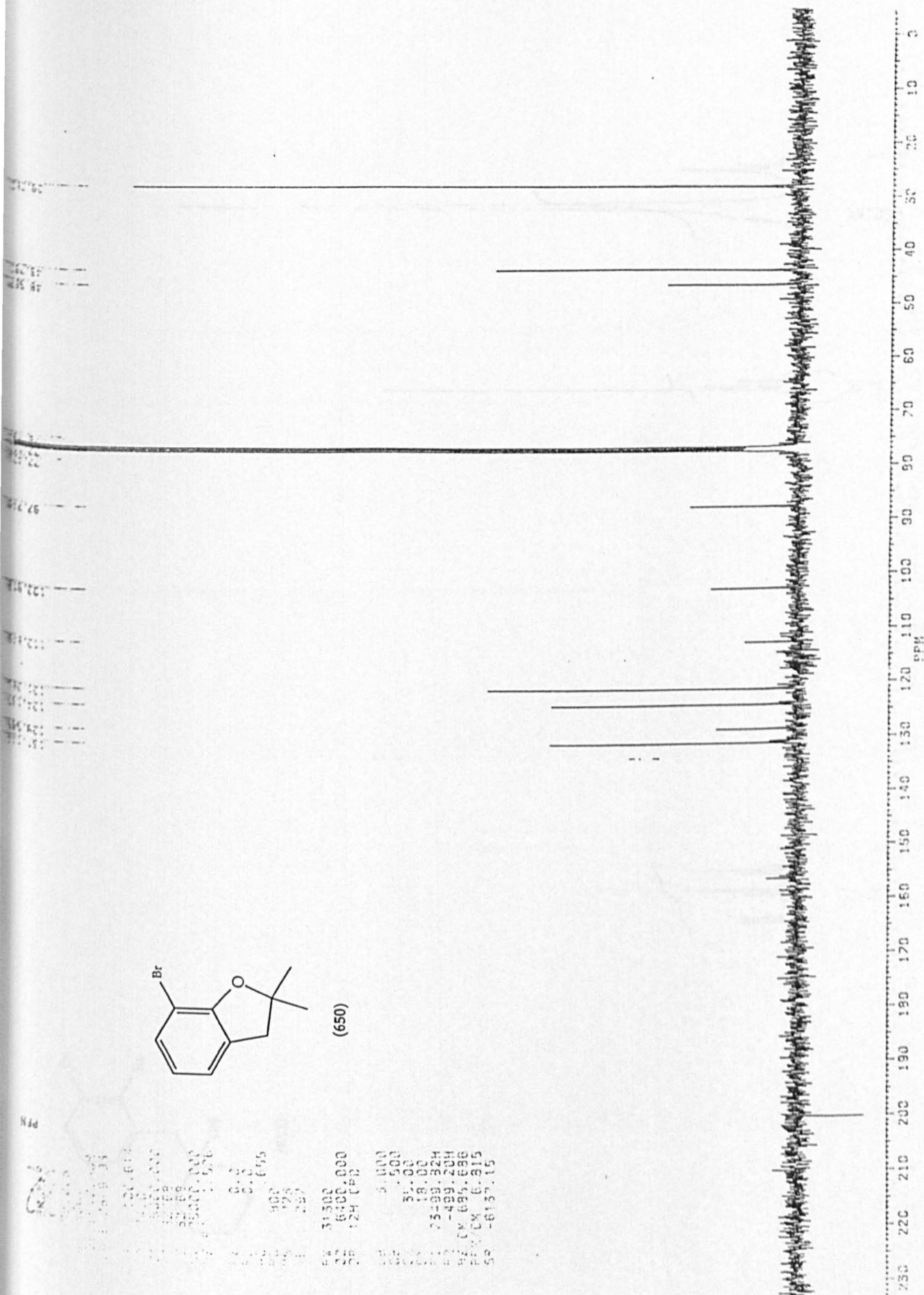
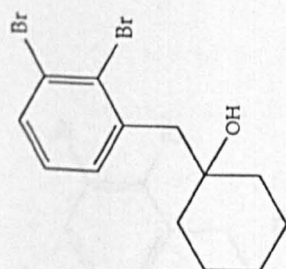


Figure 2b



(651)

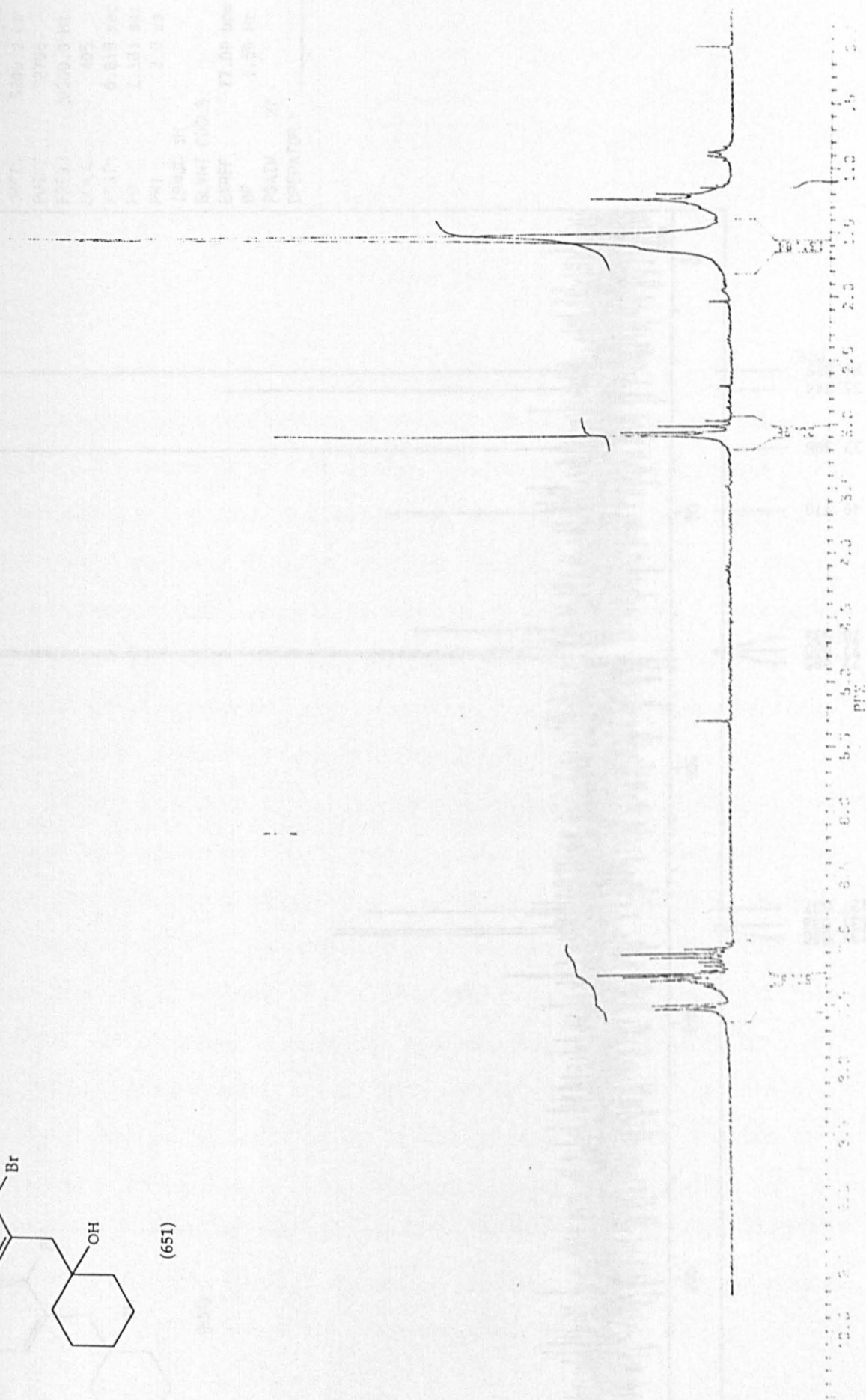


Figure 3a

OFH 67.80 MHz

ORSLT 135.00 kHz

ORFID 5200.0 Hz

POINT 32763

FREQ 20000.0 Hz

SCANS 405

AQUM 0.819 sec

PD 2.181 sec

PW1 3.8 us

IRNJC 1H

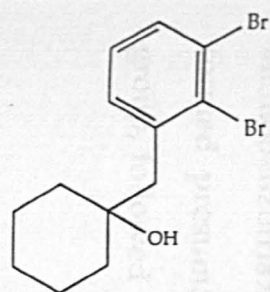
SLVNT CDCL3

EXREF 77.00 ppm

BF 1.50 Hz

PGAIN 27

OPERATOR :



(651)

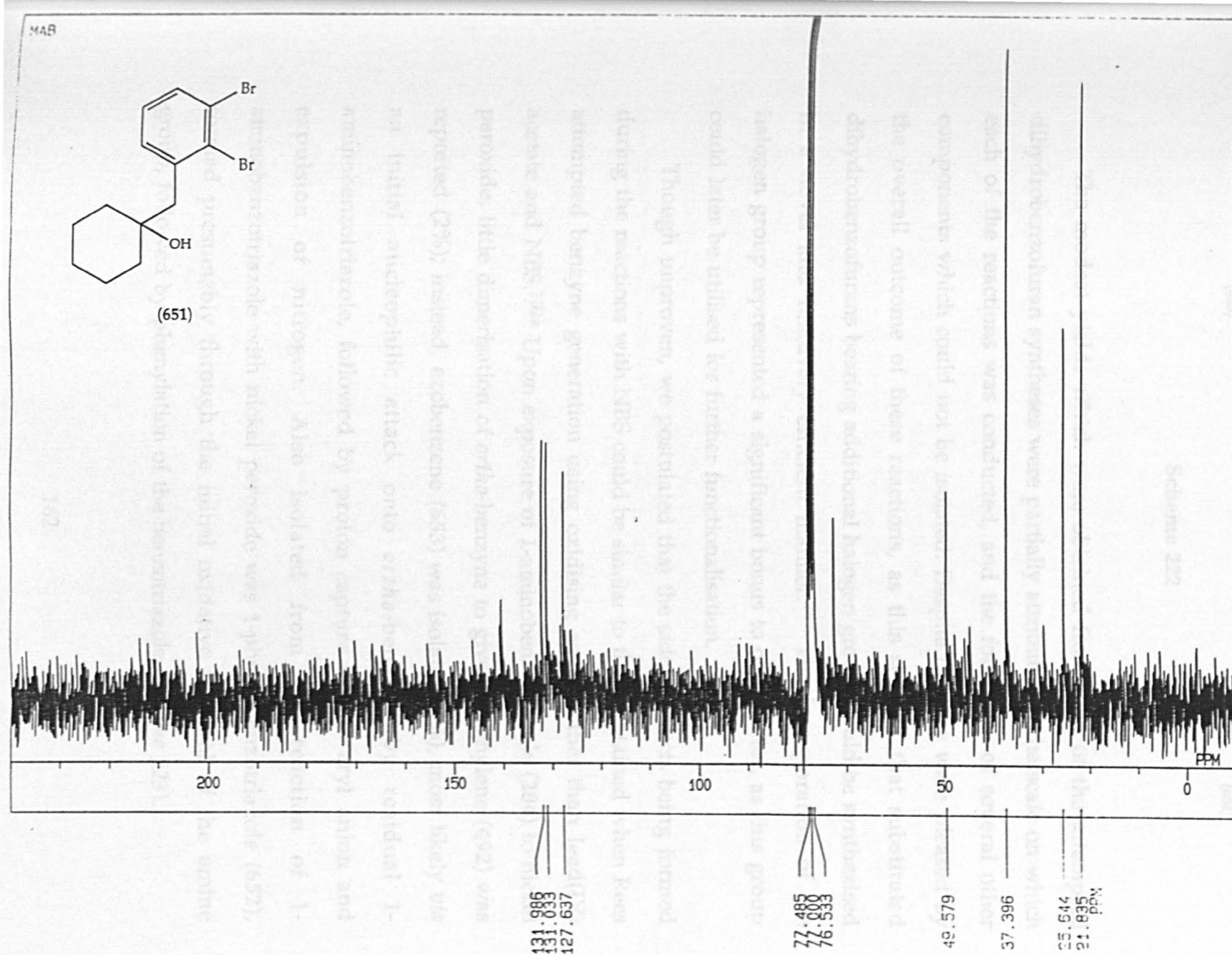
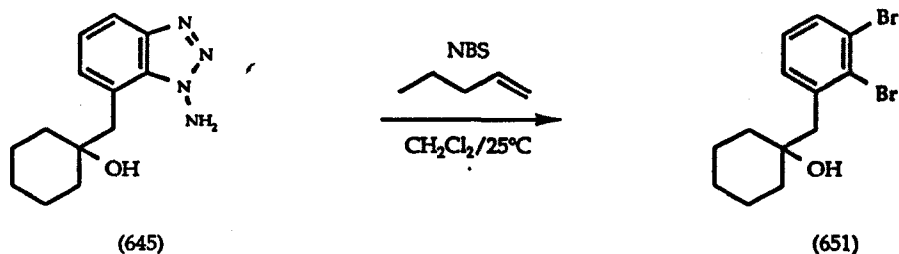


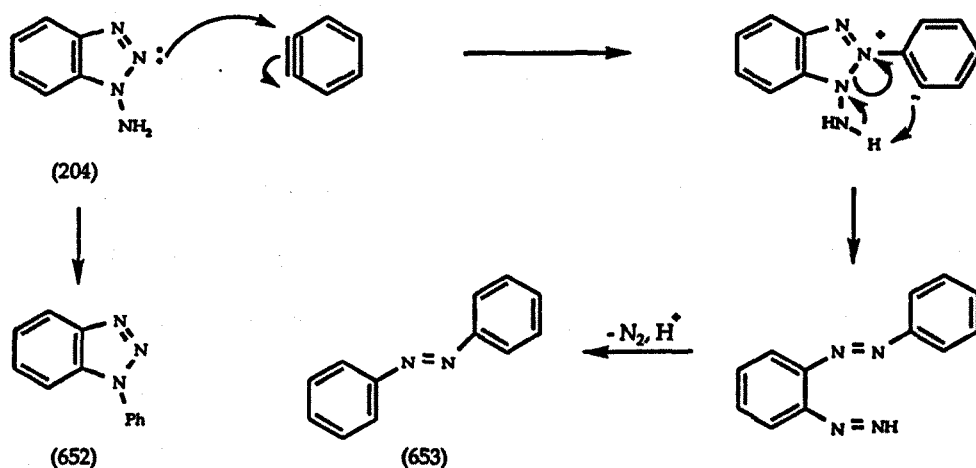
Figure 3b



Scheme 222

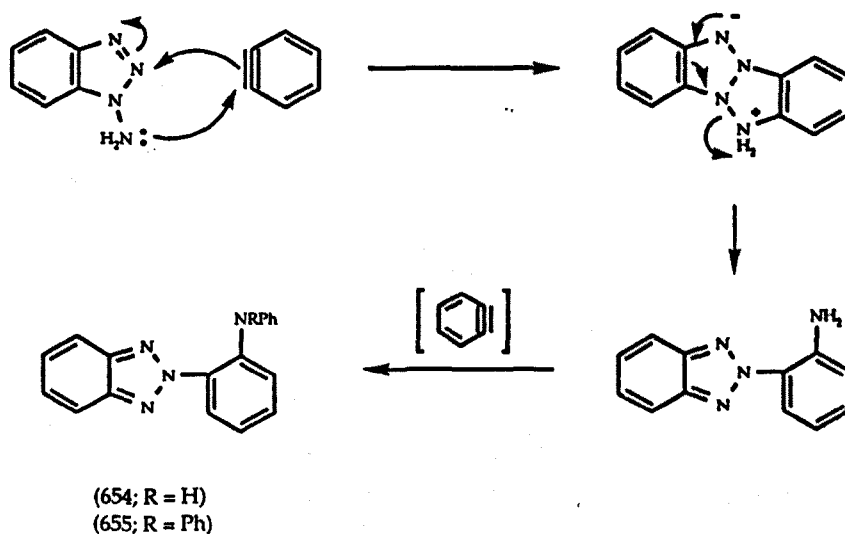
The modest yields which were obtained from each of the attempted dihydrobenzofuran syntheses were partially attributed to the scale on which each of the reactions was conducted, and the formation of several other components which could not be isolated. Despite this, we were pleased by the overall outcome of these reactions, as this showed that substituted dihydrobenzofurans bearing additional halogen groups could be synthesised in a novel and relatively efficient manner.²⁴⁷ The incorporation of the halogen group represented a significant bonus to our studies, as this group could later be utilised for further functionalisation.

Though unproven, we postulated that the side products being formed during the reactions with NBS could be similar to those obtained when Rees attempted benzyne generation using oxidising agents other than lead(IV) acetate and NBS.^{102a} Upon exposure of 1-aminobenzotriazole (204) to nickel peroxide, little dimerisation of *ortho*-benzyne to give biphenylene (492) was reported (2%); instead, azobenzene (653) was isolated (3%), most likely *via* an initial nucleophilic attack onto *ortho*-benzyne by residual 1-aminobenzotriazole, followed by proton capture by the aryl anion and expulsion of nitrogen. Also isolated from the reaction of 1-aminobenzotriazole with nickel peroxide was 1-phenylbenzotriazole (652), formed presumably through the initial oxidative removal of the amine group, followed by phenylation of the benzotriazole (Scheme 223).



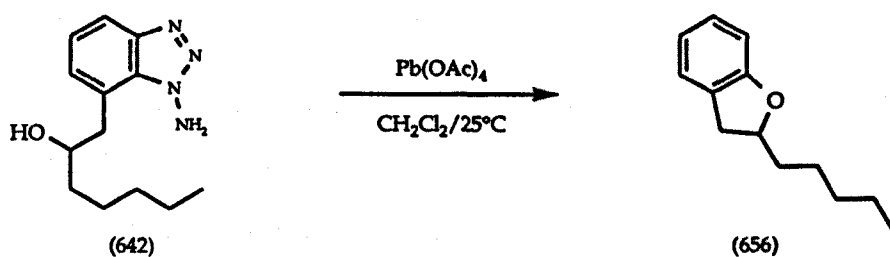
Scheme 223

Rees also reported a similar course of events to the above when benzyne generation using iodobenzene diacetate was attempted;²⁴⁸ 1,2-diiodobenzene was isolated as the major product in 70% yield, along with azobenzene (653) and 1-phenylbenzotriazole (652), again in low yields (4% and 3% respectively), and two other products, which were later identified as the *N*-phenylated aminophenylbenzotriazoles (654) and (655), formed *via* rearrangement of a zwitterion, and subsequent phenylation (Scheme 224).



Scheme 224

As mentioned previously, the most widely used reagent for benzyne generation from 1-aminobenzotriazoles has been lead(IV) acetate, which leads to benzyne formation in a rapid, clean and virtually quantitative manner. To confirm that benzyne generation from our substrates was possible using this reagent, and that dihydrobenzofuran formation could subsequently occur, two of the substrates, namely the *n*-hexanal (642) and acetone adducts (644) were exposed to this oxidising agent. The addition of the *n*-hexanal adduct to one equivalent of lead(IV) acetate in dichloromethane at ambient temperature yielded a crude material, spectroscopic analysis of which appeared to confirm the formation of the dihydrobenzofuran skeleton. High Resolution Mass Spectrometry confirmed the formation of the simple dihydrobenzofuran (656), which was isolated as a colourless oil in 65% after chromatography (Scheme 225). The improved yield using this reagent was attributed to the lack of obvious benzyne scavengers, compared to the presence of molecular bromine when using NBS. Additionally, the presence of lead cations could conceivably stabilise the benzyne prior to intramolecular trapping.^{102a}

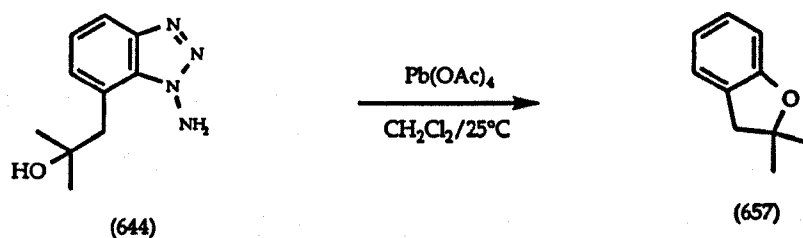


Scheme 225

The preference of the generated aryl anion to undergo simple quenching *via* proton transfer was attributed to the acidic conditions of the reaction media caused by lead(IV) acetate; attempts to inhibit proton quenching and encourage substituent incorporation in a similar manner to

that achieved using NBS, were made by repeating the reaction in the presence of potassium carbonate. However, this failed to alleviate the situation, with the simple dihydrobenzofuran (656) again being isolated in a comparable yield to before.

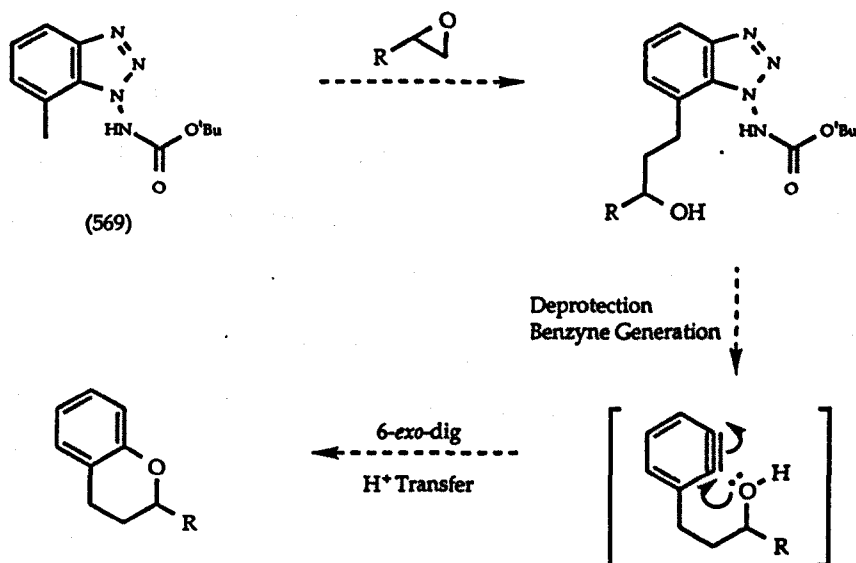
In a similar manner to the *n*-hexanal adduct, the acetone adduct (644) was exposed to lead(IV) acetate in dichloromethane at ambient temperature, with spectroscopic analysis of the crude material again indicating simple quenching of the aryl anion; this was again confirmed by High Resolution Mass Spectrometry with the resulting simple dihydrobenzofuran (657) being isolated as a colourless oil in a good yield of 75% after chromatography.²⁴⁷



Scheme 226

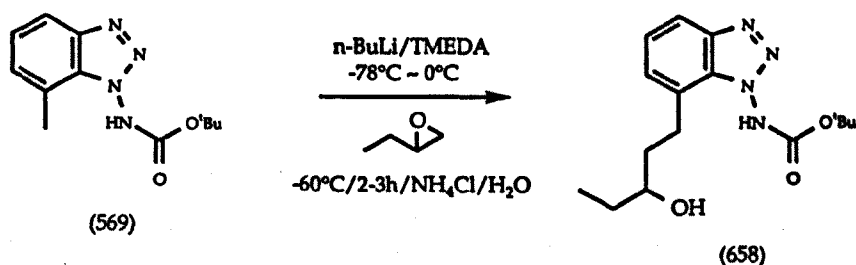
Chroman Synthesis

In a similar manner to the synthesis of 2-substituted dihydrobenzofurans described previously, construction of 2-substituted chromans appeared to be possible *via* the condensation of BOC-protected 7-methyl-1-aminobenzotriazole (569) with mono-substituted epoxides, with the BOC group being subsequently removed from the resulting homologated secondary alcohol. Benzyne generation using suitable reagents and trapping *via* a 6-*exo*-dig cyclisation would then complete the process (Scheme 227).²⁴²



Scheme 227

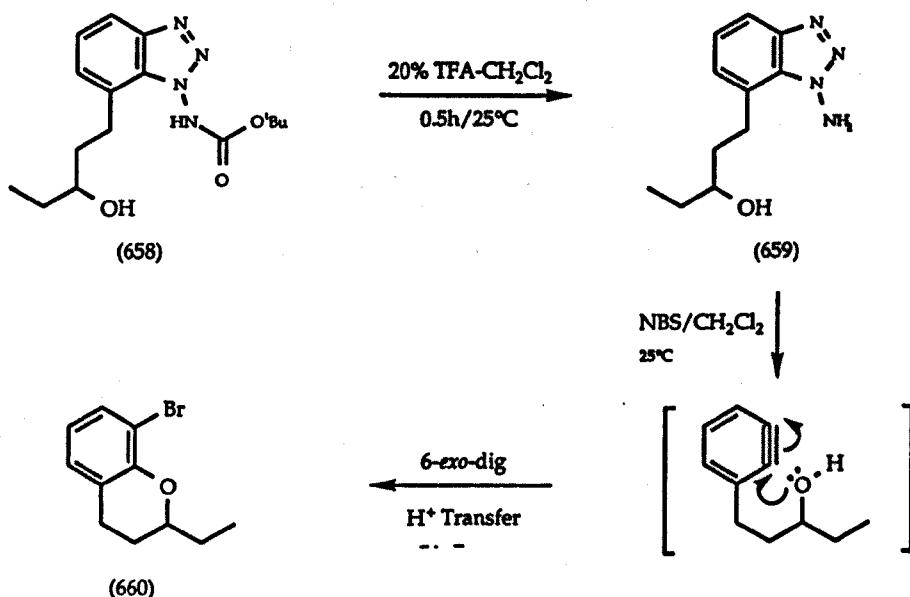
For an initial study of whether epoxides could be used as electrophiles, condensation of BOC-protected 7-methyl-1-aminobenzotriazole (569) with commercially available 1,2-epoxybutane was attempted (Scheme 228). Following the addition of the epoxide, the adduct (658) was isolated as a pale yellow oil in a very good yield of 88% after chromatography.



Scheme 228

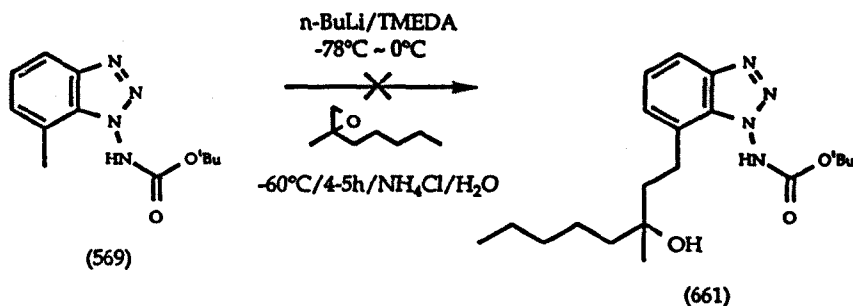
Due to a lack of possible conjugation in the corresponding alkene, the secondary alcohol in the epoxide adduct (658) appeared to be less susceptible to dehydration than the aldehyde adducts, and so a more efficient deprotection using TFA was anticipated. Accordingly, the 1-

aminobenzotriazole was isolated as a pale yellow oil in a pleasing yield of 89% after chromatography. Exposure of the adduct (659) to NBS yielded a crude material which appeared from spectroscopic analysis to contain a chroman. High Resolution Mass Spectrometry again confirmed that bromine incorporation had occurred, and following chromatography, the 2-ethyl-bromo-chroman (660) was isolated as a colourless oil in 52% yield, comparable to those yields obtained for bromo-dihydrobenzofurans.



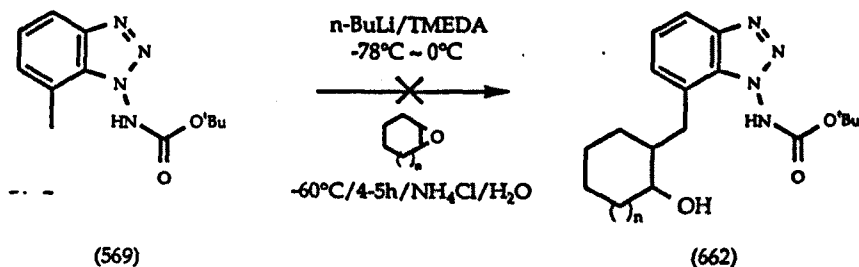
Scheme 229

In a similar manner to using ketones for the synthesis of 2,2-disubstituted dihydrobenzofurans, condensation of the BOC-protected 1-aminobenzotriazole (569) with disubstituted epoxides appeared to present a potential route to 2,2-disubstituted chromans. However, attempts to condense the 1-aminobenzotriazole with a disubstituted epoxide, derived from 2-methyl heptene, led to very little conversion into the alcohol (661), as spectroscopic analysis of the crude material failed to indicate any sign of condensation (Scheme 230).



Scheme 230

An extension of the idea of quenching with disubstituted epoxides was that condensation of (569) with cyclic epoxides could in theory eventually lead to tricyclic ring systems. However, in a similar manner to above, attempted condensation with cyclopentene ($n = 0$) and cyclohexene oxide ($n = 1$) failed to yield any of the desired secondary alcohols (662) (Scheme 231).

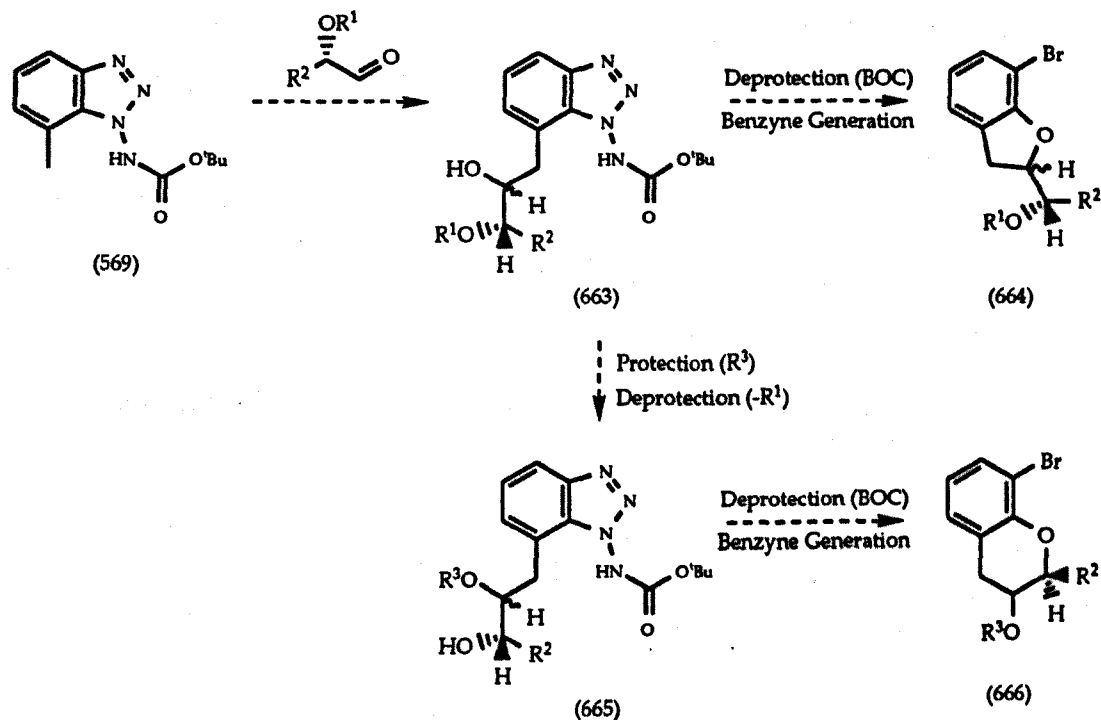


Scheme 231

Synthesis of Homochiral Dihydrobenzofurans

Using homochiral, α -substituted aldehydes as electrophiles, the relatively brief approach to dihydrobenzofurans and chromans previously described appeared to have considerable potential for the synthesis of homochiral products, with induction of chirality in the adduct (663) hopefully being achieved by either steric or complexational effects of the protecting group (R^1) on the aldehyde. Additionally, the synthesis of

homochiral chromans (666) possessing 2- and 3-substituents also appeared to be possible, by swapping the protecting groups in the initial adduct. (Scheme 232).

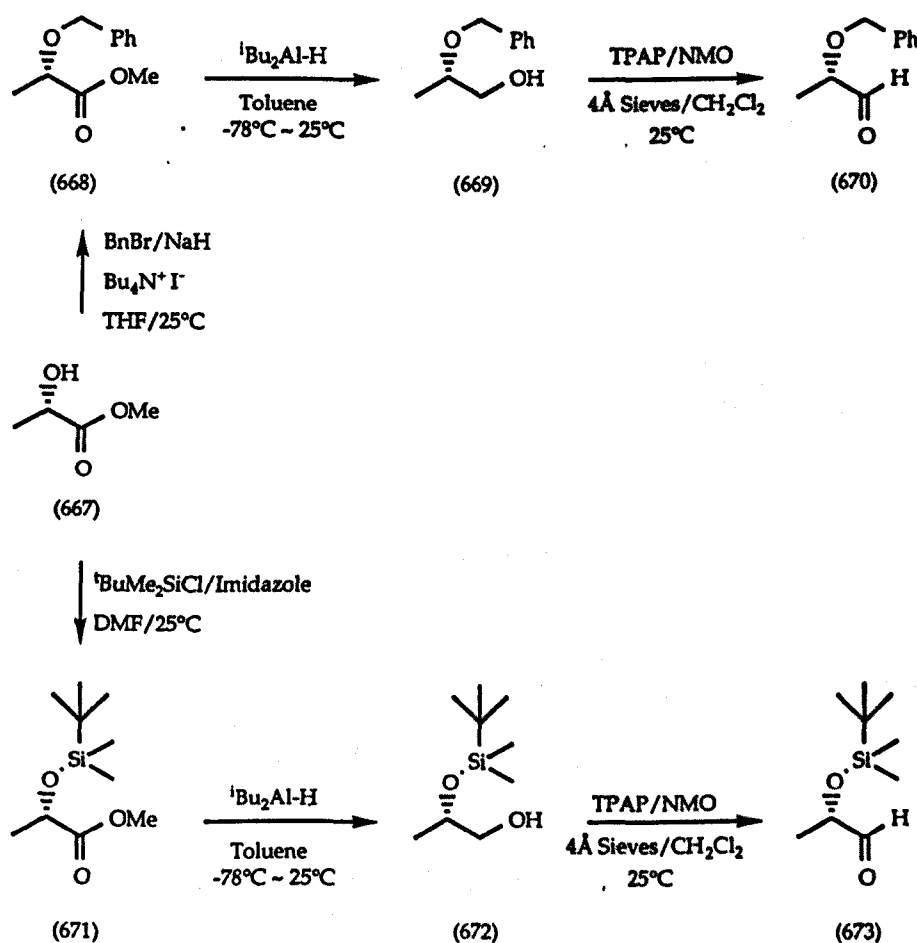


Scheme 232

For an initial investigation, the simplest homochiral aldehyde appeared to be (S)-(-)-lactaldehyde ($R^2 = CH_3$). Thus, in order to establish the viability of this scheme, the benzyl [Bn] group and *tert*-butyldimethylsilyl [TBDMS] groups were chosen to protect the hydroxyl function, primarily to highlight the differing chelating abilities that these two groups possess.²⁴⁹

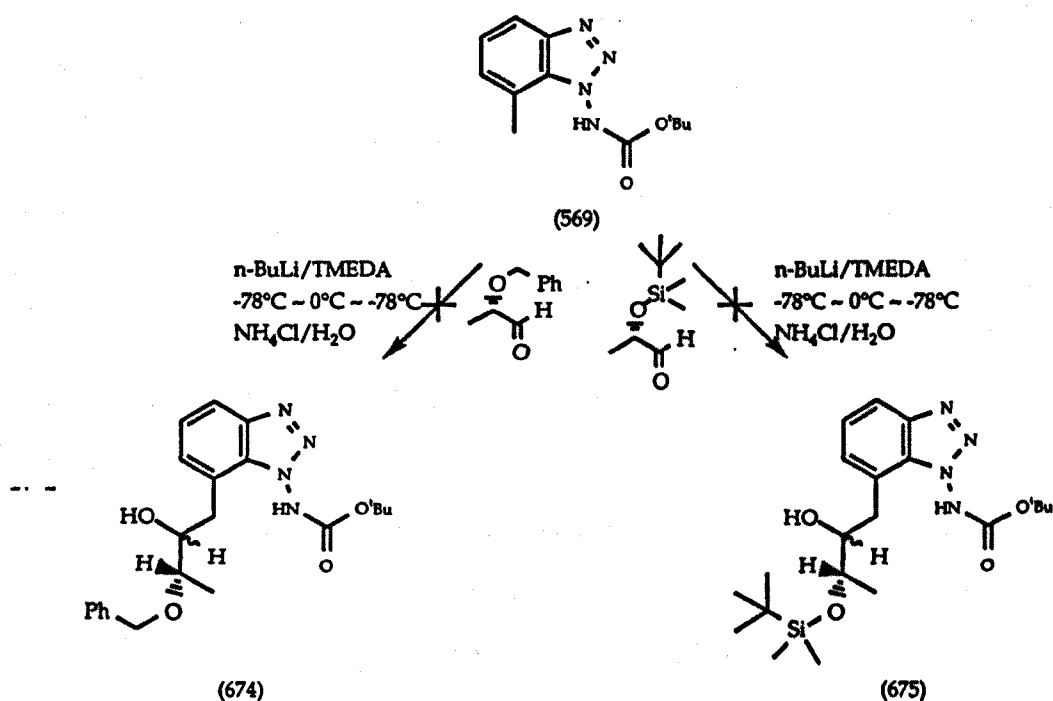
Starting from the methyl ester of (S)-(-)-lactic acid (667),²⁵⁰ benzyl protection was achieved upon stirring with sodium hydride and benzyl bromide in THF at ambient temperature, in the presence of catalytic tetra-*n*-butylammonium iodide, with the benzyl-protected methyl lactate (668) isolated as a pale yellow oil in 65% yield after chromatography. Reduction of

the ester to the alcohol (669) using DIBAL-H at -78°C gave the product as a colourless oil after chromatography in a modest yield of 42%. Oxidation of the alcohol using TPAP²³³ gave the desired benzyl-protected (S)-(-) lactaldehyde (670) as a colourless oil in a good yield of 65%. Synthesis of the *tert*-butyldimethylsilyl [TBDMS] protected (S)-(-)-lactaldehyde (673) was attempted along similar lines,²⁵⁰ with the TBDMS-protected methyl ester (671) being prepared as a colourless oil in 95% yield using TBDMS-chloride in *N,N*-dimethylformamide [DMF]. Reduction of the ester to the alcohol (672) using DIBAL-H gave the product as a pale yellow oil in 73% yield, whilst oxidation of the alcohol using TPAP gave the TBDMS-protected (S)-(-)-lactaldehyde (673) as a colourless oil in a modest yield of 35%.



Scheme 233

Attempted condensation of BOC-protected 7-methyl-1-aminobenzotriazole (569) with the benzyl-protected (S)-(-)-lactaldehyde (670) ended in complete failure, with spectroscopic analysis of the crude material suggesting that none of the desired adduct (674) had been generated; instead, an inseparable mixture of components was isolated. Similarly, condensation with TBDMS-protected (S)-(-)-lactaldehyde (673) was unsuccessful, and failure to incorporate either of the homochiral aldehydes spelled a disappointing end for this scheme (Scheme 234).



Scheme 234

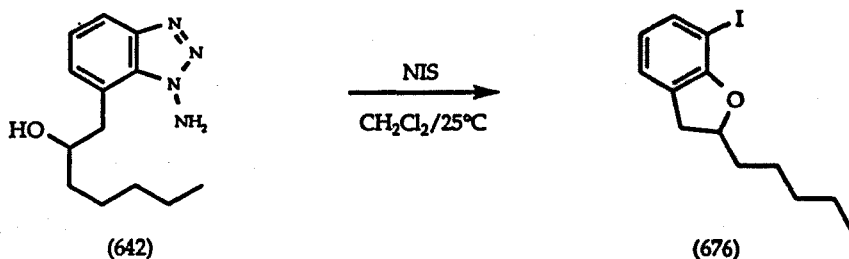
N-Iodosuccinimide - A Superior Reagent for Benzyne Generation from *ortho*-Substituted 1-Aminobenzotriazoles

With the synthesis of bromo-dihydrobenzofurans and chromans being achieved, our next aim was to highlight the synthetic potential of this incorporated halogen substituent, by utilising it for the further

functionalisation of the aromatic ring. In recent years, one of the most popular and efficient ways of achieving this has been to use either zero-valent palladium or nickel catalysts, either in aryl-aryl or aryl-alkene coupling reactions,²⁵¹ or in couplings with sp centres.²⁵² Although aryl bromides in general have been used in such couplings, a closer inspection of the coupling reactions of *ortho*-alkoxy aryl bromides suggested that couplings of such species either have to be achieved under forcing conditions, or in some instances fail completely. Additionally, *ortho*-alkoxy aryl iodides have been shown to undergo most types of couplings in an efficient manner, more so than for aryl bromides. Considering that the halogenated dihydrobenzofurans we had generated were in effect *ortho*-alkoxy aryl halides, the evidence provided by the literature suggested to us that iodinated forms of our halogenated dihydrobenzofurans and chromans would undergo coupling reactions with a greater efficiency. The question then arose of whether such iodinated species could be synthesized in a similar manner to the brominated species *i.e.* through the use of *N*-iodosuccinimide [NIS].

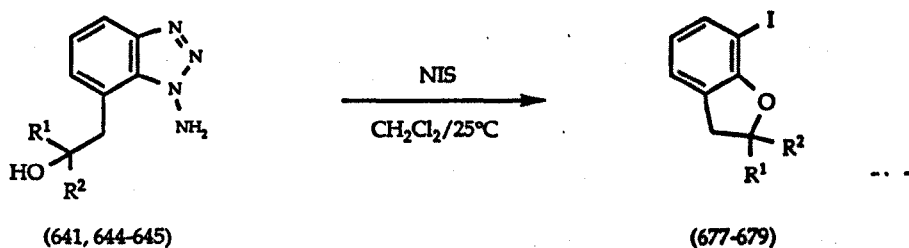
As there had been no previous reports of the use of NIS to generate benzyne from 1-aminobenzotriazoles, the conditions that were used for the NBS-induced cyclisations were initially employed. The *n*-hexanal adduct (642) was added to 2.5 equivalents of NIS in dichloromethane at ambient temperature, and was accompanied by instantaneous evolution of nitrogen and the conversion of the solution to a purple colouration, indicative of molecular iodine formation. Unlike the reaction with NBS, however, tlc analysis of the reaction mixture indicated the formation of only one component and, following aqueous thiosulphate wash to remove iodine, spectroscopic analysis of the crude material indicated the formation of the iodo-dihydrobenzofuran (676), which was isolated as a colourless oil in an excellent yield of 92%, with all spectroscopic and analytical data confirming

the incorporation of an iodine atom (*Scheme 235*).



Scheme 235

Having shown that iodo-dihydrobenzofuran synthesis could be accomplished in this spectacular manner, the other substrates that had been previously exposed to NBS were then treated with NIS, to see if similar improvements in yields could be obtained (*Scheme 236; Table 12*).



Scheme 236

R^1	R^2	<u>SUBSTRATE</u>	<u>PRODUCT</u>	<u>YIELD (%)</u>
C_6H_5	H	(641)	(677)	81
CH_3	CH_3	(644)	(678)	95
$-C_5H_{10}-$		(645)	(679)	82

Table 12; Synthesis of Iodo-Dihydrobenzofurans

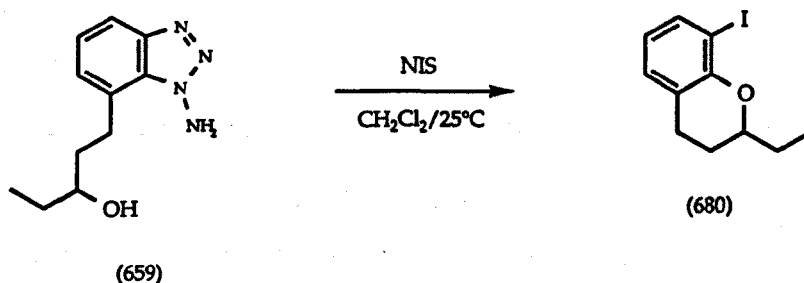
We were very pleased to find that an anticipated improvement in the

synthesis of the dihydrobenzofuran (677) resulting from cyclisation of the benzaldehyde adduct (641) was also achieved, with the product being isolated after chromatography as a colourless oil in a very good yield of 81%. More significantly, the exposure of the acetone adduct (644) and cyclohexanone adduct (645) to NIS also gave remarkably high yields of the corresponding iodo-dihydrobenzofurans after chromatography; the product (678) from the acetone adduct was isolated as a pale yellow oil in 95% yield, whilst the cyclohexanone adduct gave the spiro-iodo-dihydrobenzofuran (679) as a colourless oil in a very good yield of 82%. These two results initially surprised and delighted us, as unlike the reactions with NBS, cyclisation of the tertiary alcohols could be effected in a highly efficient manner without the requirement of a halogen scavenger. Comparison of the reactions of the cyclohexanone adduct (645) with NBS and NIS provided the greatest contrast in the effectiveness of the two reagents; with NBS, attempted cyclisation resulted in abject failure, whilst with NIS, cyclisation proceeded in excellent fashion.²⁵³

The potential of NIS to synthesize iodo-chromans in improved yields was tested using the 1,2-epoxybutane adduct (659). In a similar manner to the iodo-dihydrobenzofurans, addition of the adduct to NIS resulted in the formation of only one component, which was shown by spectroscopic analysis to be the iodo-chroman (680; *Scheme 237*). Chromatography of the crude material yielded the product as a colourless oil in 63%, a lower yield than those yields obtained for the dihydrobenzofurans (82-95%), and only a slight improvement over the yield obtained in the synthesis of the corresponding bromo-chroman (660; 52%).

Although chroman synthesis did not appear to be greatly improved by the use of NIS, a clear advantage that this reagent held was that the product was formed cleanly, and not in conjunction with a number of other

components which would require careful separation by chromatography, as was the case with NBS. Indeed, the yield may well have resulted from the small scale on which the reactions were carried out, thus increasing the range of experimental error.²⁵⁴

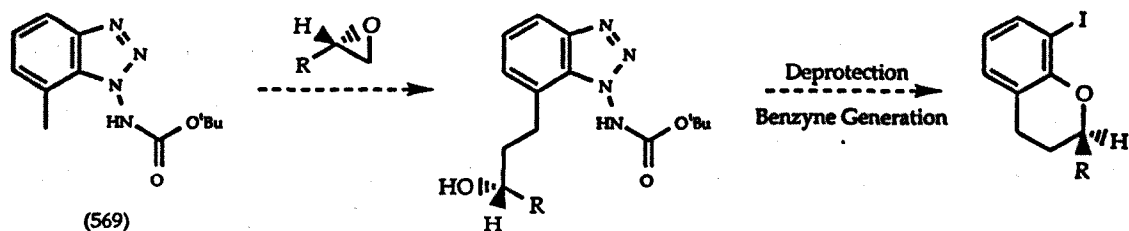


Scheme 237

The remarkably clean and high yielding reactions of the substituted 1-aminobenzotriazoles with NIS represented several important developments in the field of benzyne chemistry; firstly, they represented the first known use of NIS for benzyne generation from 1-aminobenzotriazoles, with this reagent appearing to be just as efficient as other reagents such as lead(IV) acetate. Additionally, the yields obtained appeared to represent one of the highest sets of yields for any known intramolecular benzyne trappings to date, and one of the first synthetically viable examples of intramolecular trapping of benzyne leading to benzo-fused oxygen heterocycles.

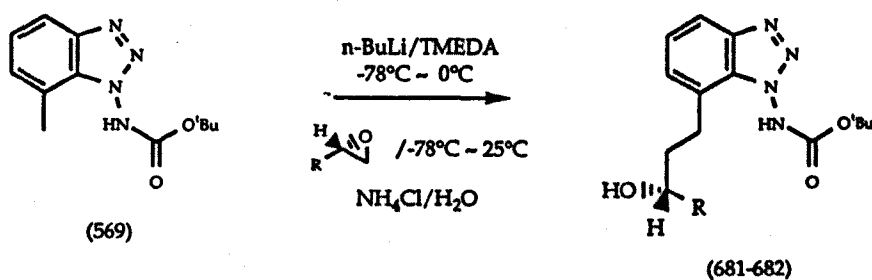
Homochiral Chroman Synthesis Using Chiral Epoxides

The preparation of homochiral iodo-chromans appeared to be possible by using commercially available homochiral epoxides as model electrophiles when functionalising BOC-protected 7-methyl-1-aminobenzotriazole (569) (Scheme 238).



Scheme 238

Condensation of BOC-protected 7-methyl-1-aminobenzotriazole (569) with commercially available (S)-(-)-propylene oxide was effected by allowing the reaction mixture to warm up gradually overnight to ambient temperature, so as to encourage complete alkylation. After doing so, the desired secondary alcohol (681) was isolated as a pale yellow gum, in 78% yield after chromatography. Similarly, condensation of (569) with (S)-(-)-styrene oxide yielded the corresponding product (682) as a pale yellow oil in a modest yield of 44% (Scheme 239; Table 13).

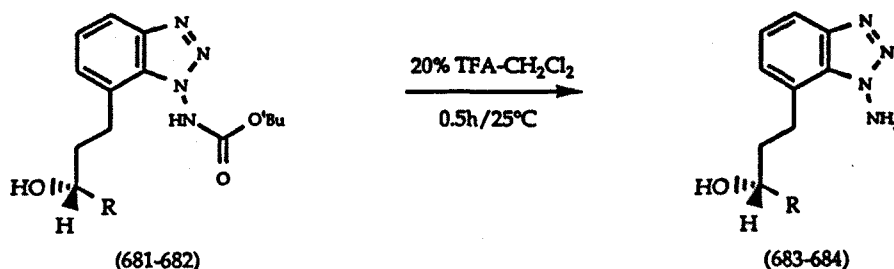


Scheme 239

<u>ELECTROPHILE</u>	<u>PRODUCT</u>	<u>YIELD (%)</u>
(S)-(-)-Propylene Oxide	(681)	78
(S)-(-)-Styrene Oxide	(682)	44

Table 13; Functionalisation of (569) with Homochiral Epoxides

Deprotection of the epoxide adducts (681) and (682) was attempted using TFA as previously described, with the (S)-(-)-propylene oxide adduct (683) being isolated as a colourless oil in 70% yield after chromatography. With the benzylic alcohol in the (S)-(-)-styrene oxide adduct (682) appearing to be susceptible to dehydration, the corresponding 1-aminobenzotriazole (684) was isolated as a colourless oil in a modest yield of 40% (*Scheme 240*).

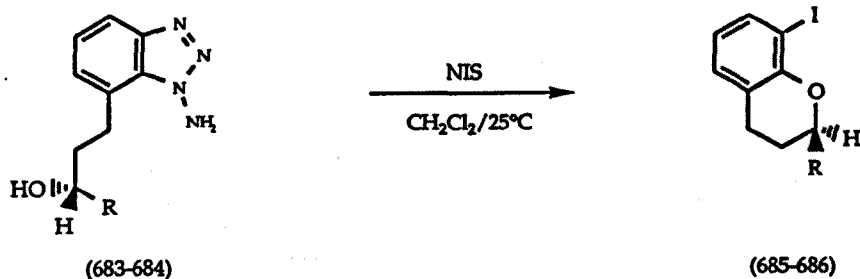


Scheme 240

<u>SUBSTRATE</u>	<u>PRODUCT</u>	<u>YIELD (%)</u>
(681)	(683)	70
(682)	(684)	40

Table 14; Deprotection of Homochiral Epoxide Adducts

We were pleased to find that the anticipated homochiral chroman synthesis could be achieved, and in a slightly improved manner over the corresponding 2-ethyl substituted chroman, due to better handling of the reaction mixture. The addition of the (S)-(-)-propylene oxide adduct (683) to NIS led to the formation of the 2-methyl-chroman (685) as a colourless oil in 68% yield after chromatography, whilst the (S)-(-)-styrene oxide adduct (684) gave the corresponding 2-phenyl-chroman (686) as a colourless oil in a similar yield of 77% (*Scheme 241*).²⁵⁴



Scheme 241

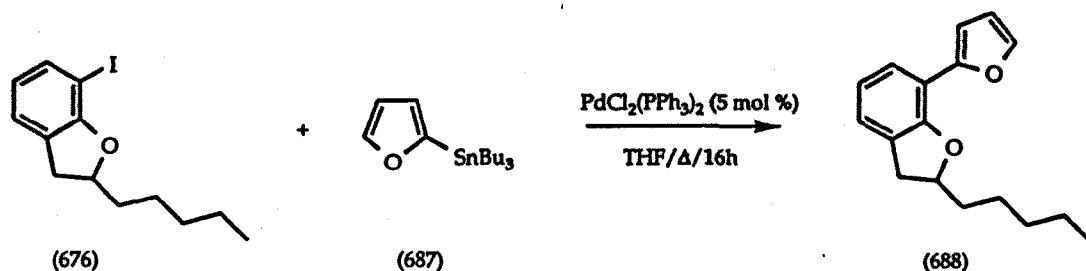
<u>SUBSTRATE</u>	<u>PRODUCT</u>	<u>YIELD (%)</u>
(683)	(685)	68
(684)	(686)	77

Table 15; Synthesis of Homochiral Iodo-Chromans

Homologation of Iodo-Dihydrobenzofurans and Iodo-Chromans

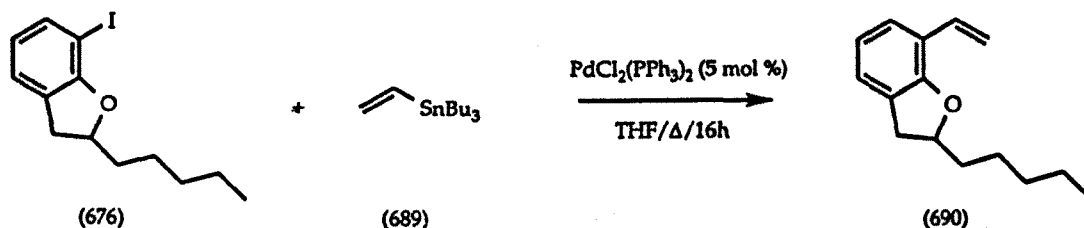
Having shown that the synthesis of dihydrobenzofurans and chromans bearing *ortho*-iodo substituents could be achieved in a highly efficient manner, the next stage was to highlight the synthetic potential of the halogen substituent as originally intended.

For the palladium(0)-catalysed aryl-aryl couplings of *ortho*-substituted aryl iodides with heteroaromatic stannanes, Bailey²⁵⁵ reported that dichloro-*bis*-(triphenylphosphine)palladium(0) [PdCl₂(PPh₃)₂] could be used as the catalytic species. Thus, aryl-aryl coupling of the 2-pentyl substituted iodo-dihydrobenzofuran (676) with 2-furyl-tri-*n*-butylstannane (687),²⁵⁶ yielded the biaryl product (688) as a colourless oil after chromatography in a low yield of 30%, a probable consequence of the small scale on which the reaction was performed (Scheme 242).



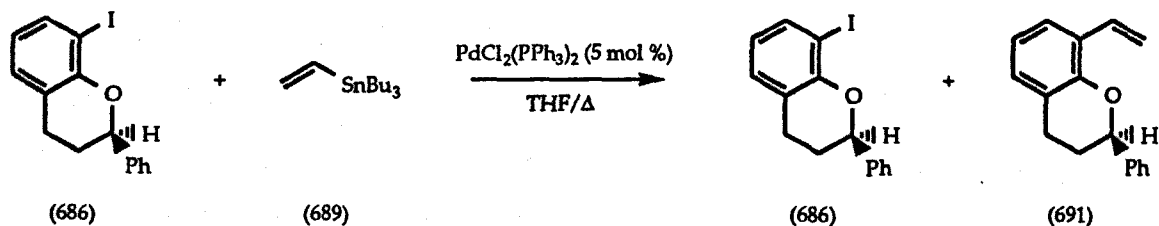
Scheme 242

For the palladium(0)-catalysed aryl-alkenyl couplings of aryl halides with vinyl stannanes leading to styrene formation, the same catalyst and conditions as those used for aryl-aryl couplings were employed, with vinyltri-*n*-butylstannane (689) being used as the alkene partner.²⁵⁷ Subsequent refluxing in THF for the same amount of time as used above yielded the desired styryl dihydrobenzofuran (690) as a colourless oil, in a highly satisfactory yield of 87% after chromatography (Scheme 243).



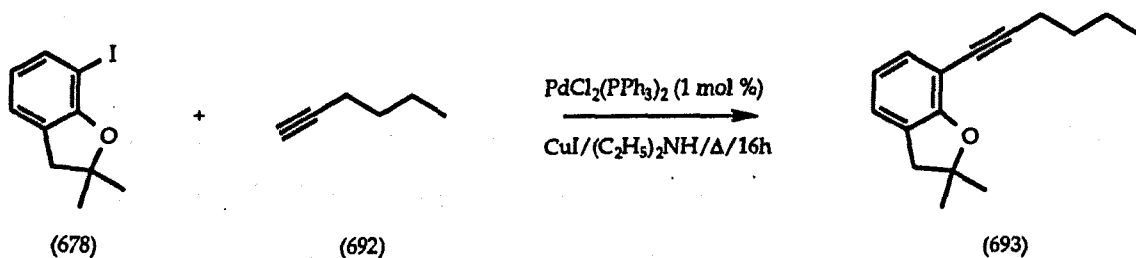
Scheme 243

To illustrate that iodo-chromans could take part in similar aryl-alkene couplings, an attempt was made to couple the iodo-chroman (686) with vinyltri-*n*-butylstannane (689) in a similar manner to above (Scheme 244). However, complete conversion failed to occur, even after the addition of further equivalents of the catalyst, with an inseparable mixture of the iodo-chroman (686) and the expected styryl chroman (691) being isolated instead.



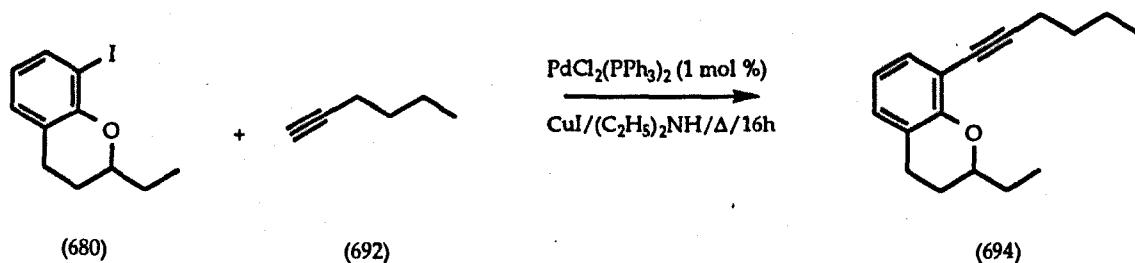
Scheme 244

Using 1-hexyne as the acetylenic species in an $\text{sp}^2\text{-sp}$ coupling,²⁵⁸ we were pleased to find that coupling with the iodo-dihydrobenzofuran (678) yielded the corresponding acetylenic dihydrobenzofuran (693) as a pale yellow oil in another pleasing yield of 80% after chromatography (Scheme 245).



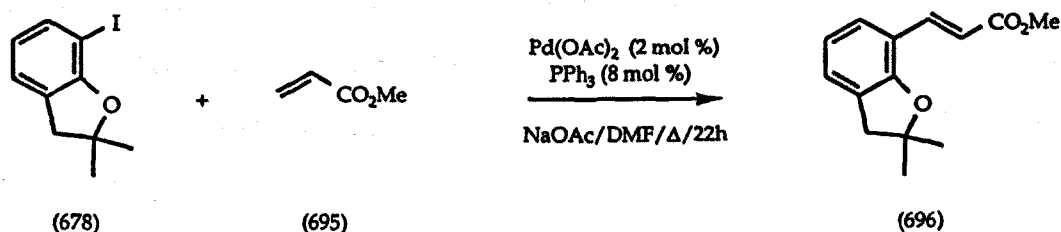
Scheme 245

Similar to above, the iodo-chroman (680) was refluxed in diethylamine in the presence of 1-hexyne and catalytic $\text{PdCl}_2(\text{PPh}_3)_2$, with the acetylenic chroman (694) being isolated as a pale yellow oil after column chromatography, in a comparable yield of 75% (Scheme 246).



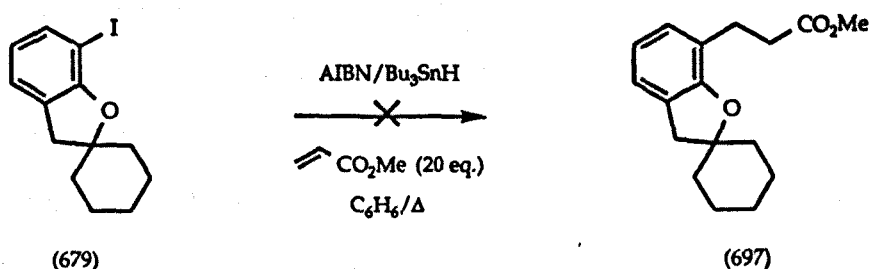
Scheme 246

The final type of palladium-catalysed coupling that was studied concerned the Heck-type coupling of aryl halides with acrylates, leading to the formation of cinnamates.²⁵⁹ Using a modified procedure,²⁶⁰ coupling of the iodo-dihydrobenzofuran (678) with methyl acrylate (695) gave the desired cinnamic ester (696) as a pale yellow oil in 62% yield following chromatography (Scheme 247).



Scheme 247

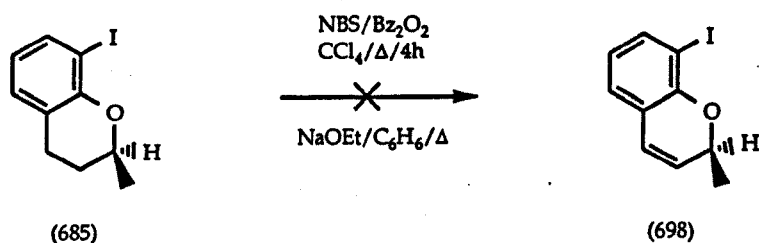
For an alternative to the palladium(0) couplings which had been previously studied, an aryl radical-mediated coupling was also attempted on the spiro-iodo-dihydrobenzofuran (679). However, attempted radical generation from this substrate using standard radical generating conditions,²⁶¹ consisting of refluxing of the dihydrobenzofuran in benzene in the presence of azo-bis-isobutyronitrile [AIBN], tri-*n*-butyltin hydride, and an excess of a Michael acceptor in the form of methyl acrylate, failed to give the corresponding product (697) (Scheme 248).



Scheme 248

Attempted Chromene Formation from Chromans

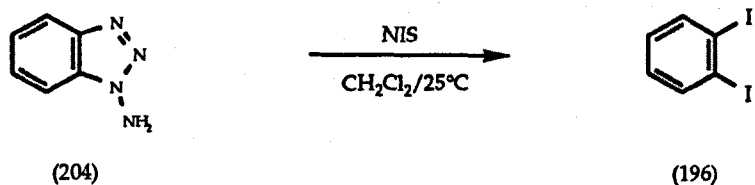
Using a literature procedure for the conversion of chromans to chromenes,²⁶² a feasibility study into the preparation of iodo-chromenes from the corresponding iodo-chromans was conducted. Thus, the iodo-chroman (685) was stirred with NBS in refluxing carbon tetrachloride [CCl_4] in the presence of benzoyl peroxide. After cooling, the mixture was evaporated, the residue taken up in benzene and solid sodium ethoxide added. Unfortunately, upon reflux an inseparable number of components were isolated, none of which appeared to be the desired product (698) (Scheme 249).



Scheme 249

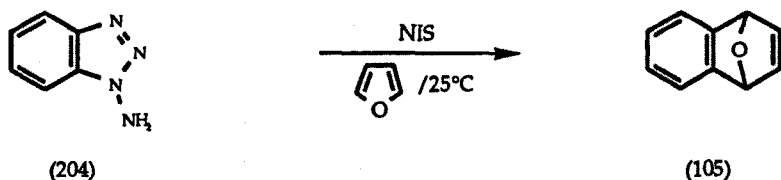
Reactions of 1-Aminobenzotriazole (204) with NIS

In order to establish the general behaviour of NIS towards 1-aminobenzotriazoles, and therefore be able to compare its reactivity with other oxidising agents such as lead(IV) acetate and NBS, the parent 1-aminobenzotriazole (204) was prepared from *ortho*-nitroaniline^{102a} and exposed to NIS. Thus, without the presence of a benzyne trap, exposure of 1-aminobenzotriazole (204) to NIS gave a crude material which was shown to be 1,2-diiodobenzene (196), chromatography of which yielded the pure product as a thick orange-brown gum in 54% yield (Scheme 250).



Scheme 250

Repeating the addition of 1-aminobenzotriazole (204) to NIS using furan as solvent, the crude material isolated was shown to be the anticipated Diels-Alder cycloadduct (105), which was obtained as off-white crystals in 49% yield after chromatography (Scheme 251).

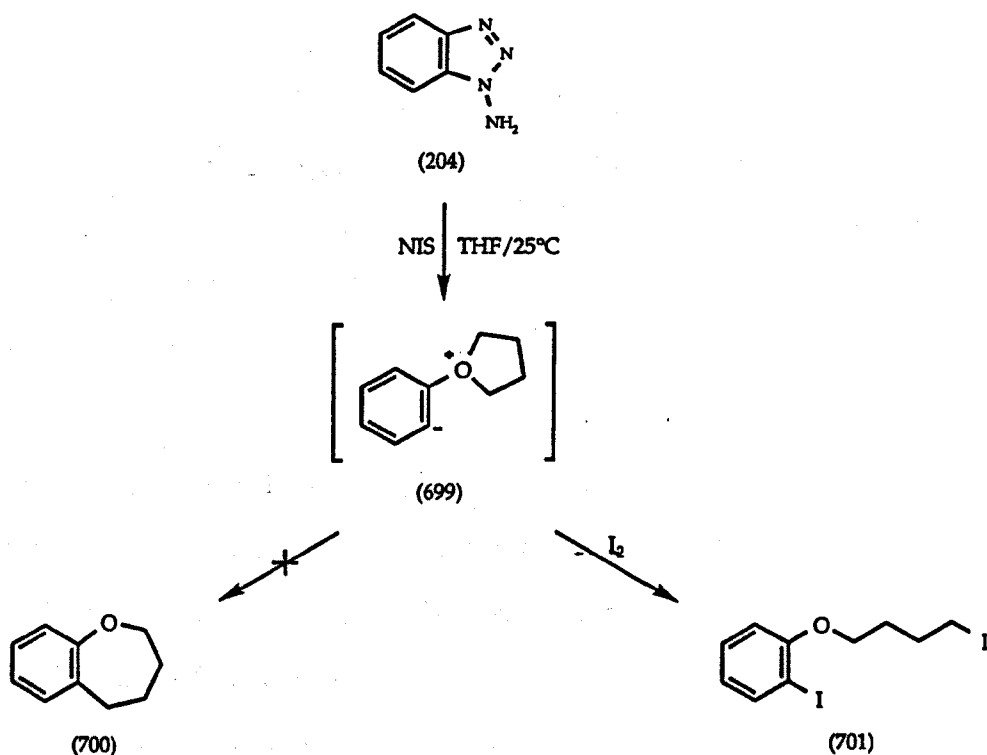


Scheme 251

Trapping of Benzyne by Cyclic Ethers

As part of our investigations into the behaviour of NIS towards 1-aminobenzotriazole (204), a brief study into the behaviour of *ortho*-benzyne in the presence of cyclic ethers was undertaken. Initially, 1-aminobenzotriazole was added to a solution of NIS in THF, with spectroscopic analysis of the crude material suggesting the formation of a number of virtually inseparable components. From this mixture, the only product isolated after chromatography appeared to be a benzosuberan ring system (700) formed *via* a rearrangement of a zwitterionic intermediate (699). However, High Resolution Mass Spectrometry of the purified orange gum showed the incorporation of two iodine atoms, with the product later

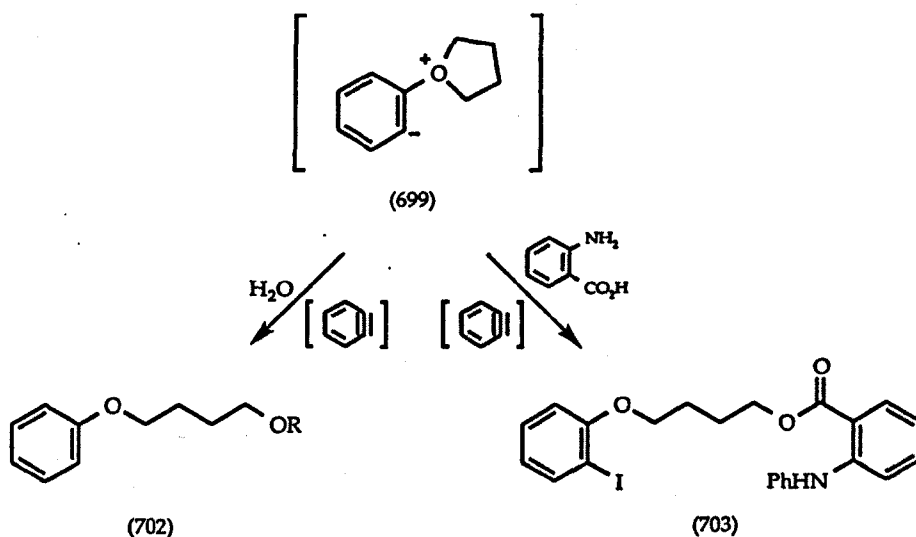
being correctly assigned as the *bis*-iodinated ether (701), isolated in a poor yield of 14%. The formation of the *bis*-iodinated product was again rationalised by the generation of a zwitterionic intermediate (699), and trapping of this species with *in situ* generated molecular iodine, whilst the low yield obtained could be explained by the poor nucleophilicity of the oxygen heterocycle in an intermolecular process, compared to that found in hydroxyl functions in our intramolecular studies.



Scheme 252

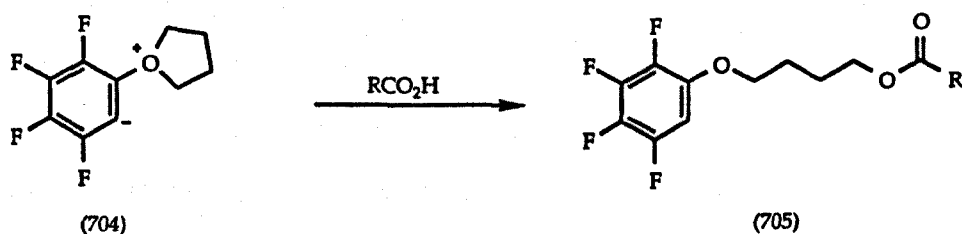
Products similar to (701) have been isolated, also in low yields, in other reports of benzyne trapping by THF; for instance, in the reaction of *ortho*-benzyne generated from anthranilic acid.²⁶³ In the presence of water, the zwitterionic intermediate (699) rearranges to give the alcohol (702, R = H) in 23% yield, and the phenyl ether (702, R = Ph) in 8% yield through further attack onto *ortho*-benzyne, whilst under anhydrous conditions the main

product (703) was formed in 17% yield *via* the reaction of the zwitterionic intermediate (699) with anthranilic acid and further phenylation by *ortho*-benzyne (Scheme 253).



Scheme 253

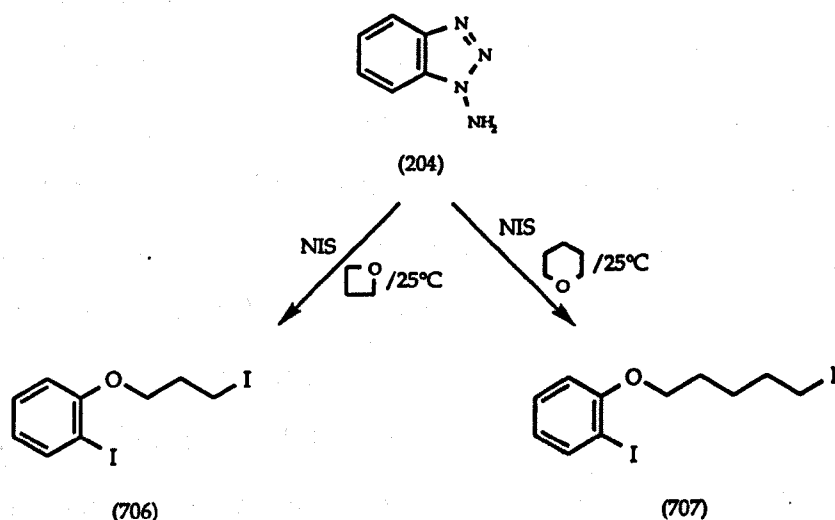
The attack of THF onto 1,2,3,4-tetrafluorobenzene (704) leading to the formation of a zwitterionic intermediate has also been reported.²⁶⁴ Following initial attack of THF, the intermediate is then attacked by externally added carboxylic acids, with rearrangement leading to the formation of ester (705) (Scheme 254).



Scheme 254

For a comparison of the reactivity of *ortho*-benzyne towards other

cyclic ethers, 1-aminobenzotriazole (204) was added to separate solutions of NIS in oxetane and tetrahydropyran [THP]. In a similar manner to above, the corresponding *bis*-iodinated ethers (706) and (707) were isolated, in 30% and 24% yields respectively (Scheme 255).



Scheme 255

e) Summary

During the course of the studies which have been conducted in Chapters Five and Six, significant progress has been made into utilising the potential of benzyne in organic synthesis.

The previously reported synthesis of 7-methyl-1-aminobenzotriazole (569) was modified and improved such that subsequent studies could be achieved. More importantly, for the construction of *ortho*-substituted 1-aminobenzotriazoles, the first examples of the metallation and functionalisation of the 1-aminobenzotriazole ring system were reported, thus providing an important contribution to the field of heterocyclic chemistry. Although the yields of condensations and BOC deprotection were slightly lower than desired, these were possibly a consequence of each

reaction being performed on small scale; opportunities to repeat these reactions on a larger scale should, in most cases, result in their optimisation.

The syntheses of dihydrobenzofurans and chromans represents the first examples of utilising 1-aminobenzotriazoles as benzyne precursors in any form of intramolecular benzyne cyclisation/cycloaddition process, and the application of the intramolecular trapping of benzyne to a relatively short, mild and efficient general route to potentially active heterocyclic species and 1,2,3-trisubstituted aromatic species. Additionally, these studies represent one of the few reported examples of intramolecular trapping of benzyne by oxygen nucleophiles, and one of the first and most efficient examples of trapping by hydroxyl functions.

Finally, the first use of NIS as a reagent for benzyne generation from 1-aminobenzotriazoles reaffirmed that these precursors should be considered as highly efficient sources of benzyne, and have the potential to be applied in a wide range of synthetic schemes, provided the appropriate reagents are used.

f) Future Work

The Construction of Dihydrobenzofuran and Chroman Precursors via Palladium(0)-Catalysed Coupling Reactions

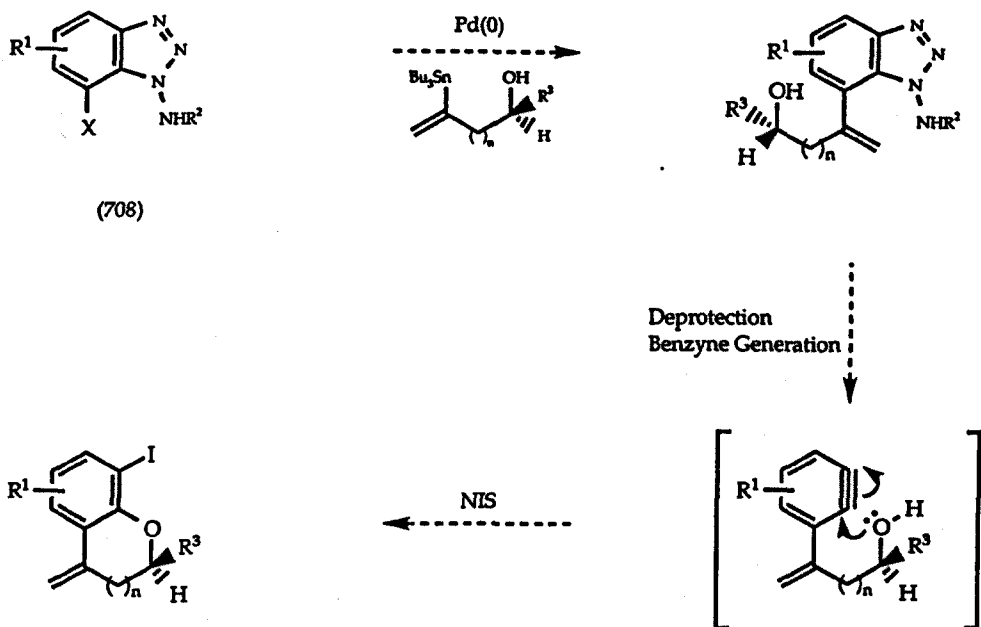
Having described the construction of dihydrobenzofuran and chroman precursors *via* the metallation and functionalisation of 7-methyl-1-aminobenzotriazole derivatives, an alternative route to such precursors, which would theoretically be more convenient, would be to 'clip' together substituted 1-aminobenzotriazole derivatives with an unsaturated species containing a suitably positioned oxygen nucleophile *via* palladium(0)-

catalysed coupling chemistry, either in the form of Stille-type couplings or *via* acetylenic couplings.

(i) *Construction via Stille-type Coupling*

Having previously shown that *ortho*-substituted aryl iodides could take part in Stille-type couplings, construction of either dihydrobenzofuran ($n = 0$) or chroman ($n = 1$) precursors appears to be possible *via* the Stille-type coupling of halogenated 1-aminobenzotriazole derivatives (708) ($X = \text{Br}, \text{I}$) or related triflates ($X = \text{OTf}$) with stannylated alcohols ($R^3 = \text{alkyl, aryl}$) (Scheme 256). Synthesis of the halogenated 1-aminobenzotriazoles should be possible by applying the route taken to synthesize 7-methyl 1-aminobenzotriazole (569), or in the case of the triflate substituent, preparation of the phenolic 1-aminobenzotriazole ($X = \text{OH}$) prior to triflate incorporation. Removal of the protecting group and benzyne generation using NIS should then lead to very clean, efficient and high yielding syntheses of iodo-dihydrobenzofurans or iodo-chromans.

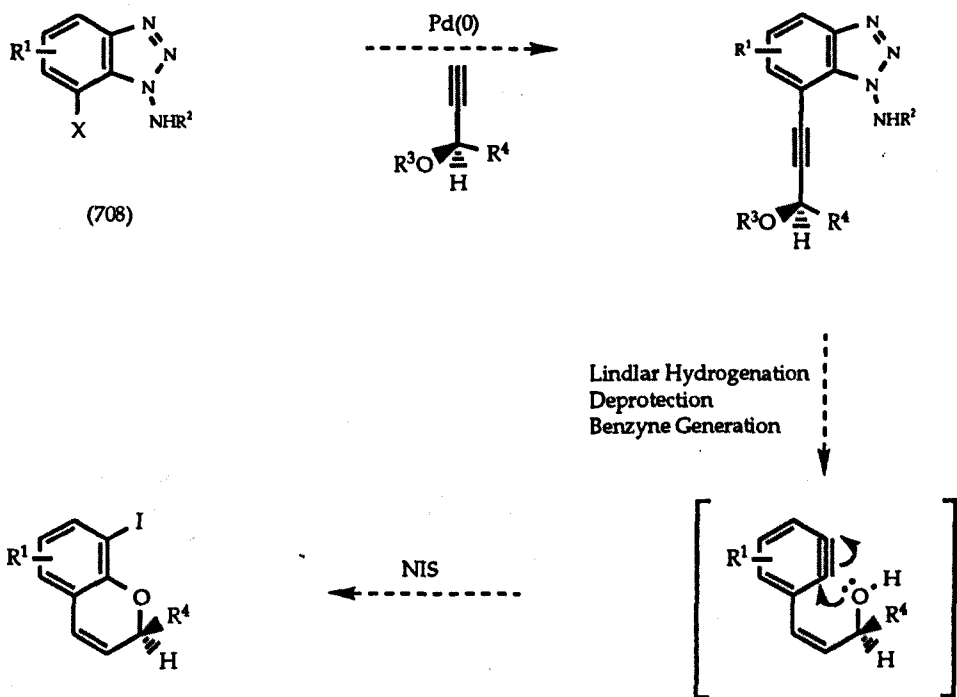
Several features of this scheme appear to make this route very attractive; firstly, the lack of metallations opens the door for using a whole range of suitable amine protecting groups which previously could not be used because of their instability towards organolithium bases. Additionally, the use of chiral, stannylated alcohols appears to give potentially rapid access to homochiral forms of both dihydrobenzofurans and chromans. Finally, the presence of an *exo*-methylene group on the heterocyclic ring also has potential for further functional group manipulation within the oxygen heterocycle, thus providing a potential route to a whole range of dihydrobenzofuran and chroman derivatives.



Scheme 256

(ii) 4H-Chromene Construction via Acetylenic Coupling Reactions

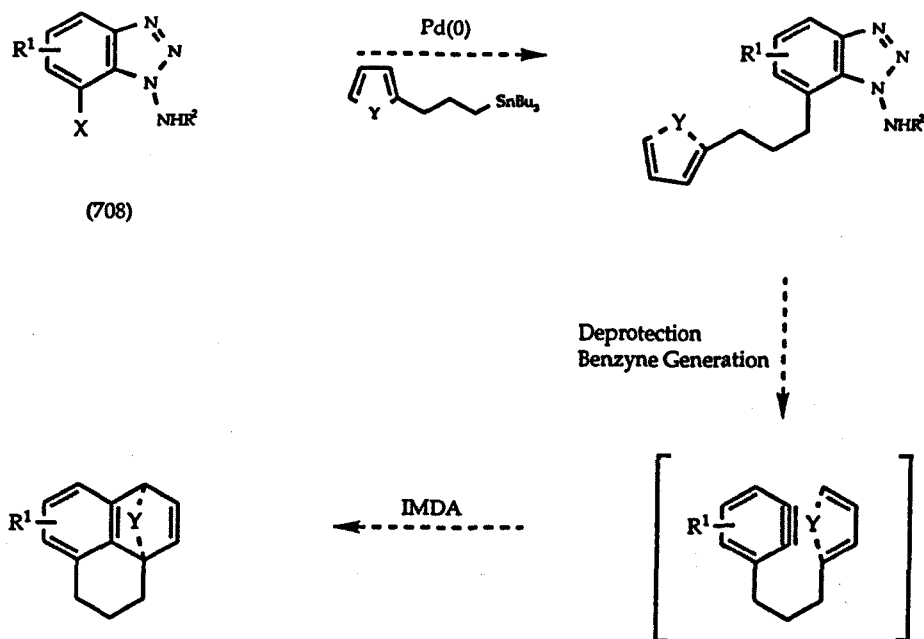
The successful acetylenic couplings of *ortho*-substituted aryl iodides with 1-hexyne suggest that similar couplings of substituted 1-aminobenzotriazole derivatives (708) ($X = \text{Br}, \text{I}, \text{OTf}$) with protected, propargylic alcohols could be achieved *via* palladium(0)-catalysed couplings. Lindlar hydrogenation of the acetylenic bond followed by deprotection and benzyne generation using NIS should then provide a clean, high yielding route to 4H-chromenes (Scheme 257). In a similar manner to the Stille-type pathway, it should be possible to use a whole range of amine protecting groups, and the preparation of homochiral products should be possible by using homochiral acetylenic secondary alcohols ($R^3 = \text{alkyl, aryl}$). The presence of the unsaturated bond in the heterocyclic ring would provide a site for the incorporation of further functionality, and potentially give access to a whole range of chroman derivatives.



Scheme 257

Construction of IMDA Precursors *via* Palladium(0)-Catalysed Couplings

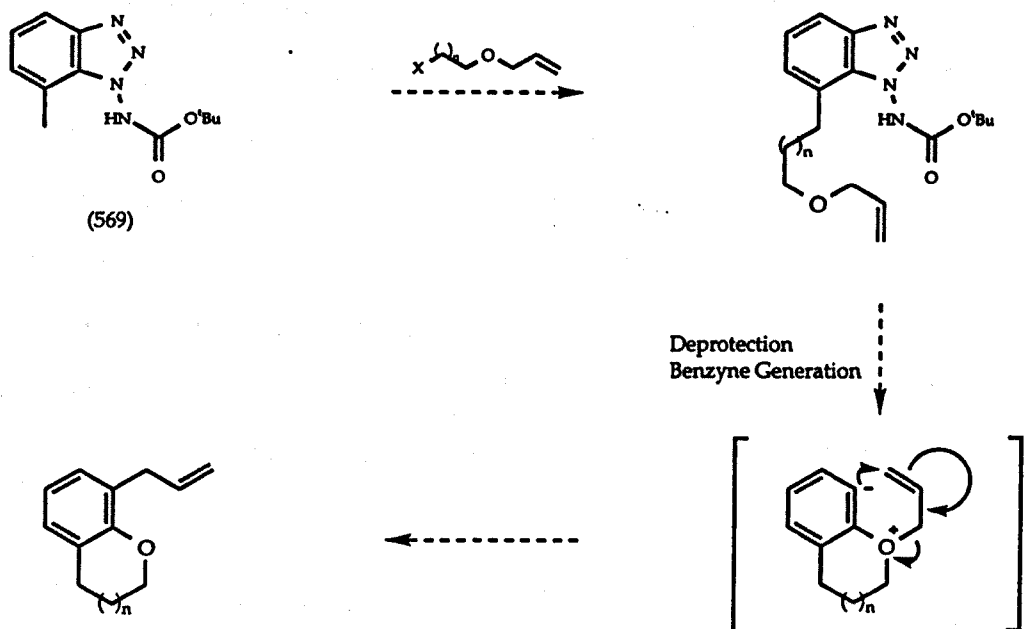
In a similar manner to that outlined above, the construction of IMDA precursors should be possible *via* the coupling of halogenated or triflyl-1-aminobenzotriazole derivatives (708) with stannylated acyclic/cyclic 1,3-diene containing moieties (Scheme 258). However, with the generation of benzyne from 1-aminobenzotriazoles in the presence of stoichiometric quantities of 1,3-dienes leading to the formation of the corresponding 1,2-dihaloarenes rather than cycloadducts when using either NBS or NIS, the use of either reagent has to be precluded. Rickborns' dual-pump syringe procedure,¹⁸³ which allows cycloadditions between benzyne (generated from 1-aminobenzotriazole), and 1,3-dienes to occur instead of biphenylene formation when using lead(IV) acetate as the reagent, appears to be the most suitable for this intended scheme.



Scheme 258

Construction of Allylic Dihydrobenzofurans and Chromans via a Tandem Addition-Rearrangement Pathway

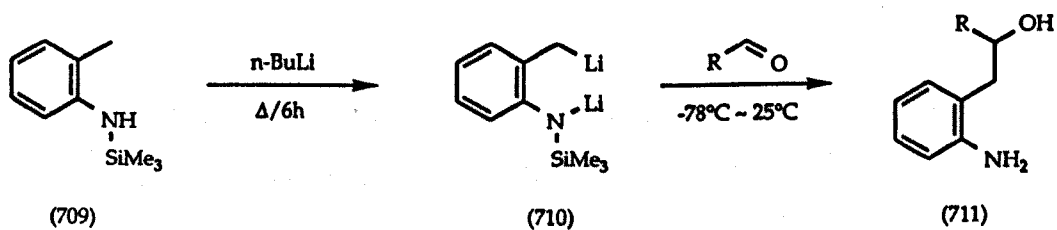
In an analogous process to the intramolecular trapping of benzyne by hydroxyl functions, the synthesis of allyl-substituted dihydrobenzofurans ($n = 0$) and chromans ($n = 1$) appears to be possible *via* the concerted or non-concerted intramolecular trapping of benzyne by allylic ethers, followed by a subsequent rearrangement. The allyl group could serve as a useful synthetic tool for functional group manipulation, in a similar manner to using halogen substituents (Scheme 259). Rickborns' dual-pump addition of lead(IV) acetate again appears to be the most suitable procedure for benzyne generation, as both NBS and NIS could possibly interfere with the tandem addition-rearrangement, either at the intramolecular trapping stage, or at the rearrangement stage, if the overall process proceeds in a non-concerted manner.



Scheme 259

The Use of Alternative Amine Protecting Groups For Metallation

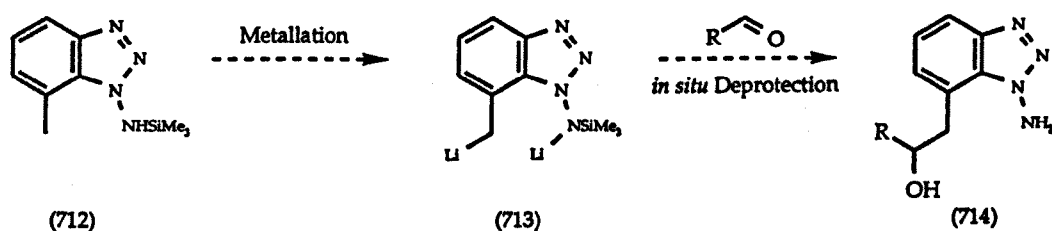
A report by Smith *et al*²⁶⁵ showed that the metallation of *ortho*-substituted aromatic sp^3 centres of silylated anilines (709) could be effected upon exposure to *n*-butyllithium, with the dianionic intermediate (710) being quenched with aldehydes, and the silyl group removed upon work-up to yield functionalised anilines (711) (Scheme 260).



Scheme 260

By protecting 7-methyl-1-aminobenzotriazole with a trimethylsilyl

group to give compound (712), it may be possible to generate the corresponding dianion (713) under similar conditions and functionalise the methyl substituent in a similar manner to that described previously, and thus incorporate the hydroxyl functionality leading to dihydrobenzofuran and chroman synthesis. The attractive feature of this route would be the *in situ* removal of the TMS group, providing an effective one-pot procedure for the synthesis of *ortho*-substituted benzyne precursors, a clear advantage over the use of the BOC group used in the present work (Scheme 261).

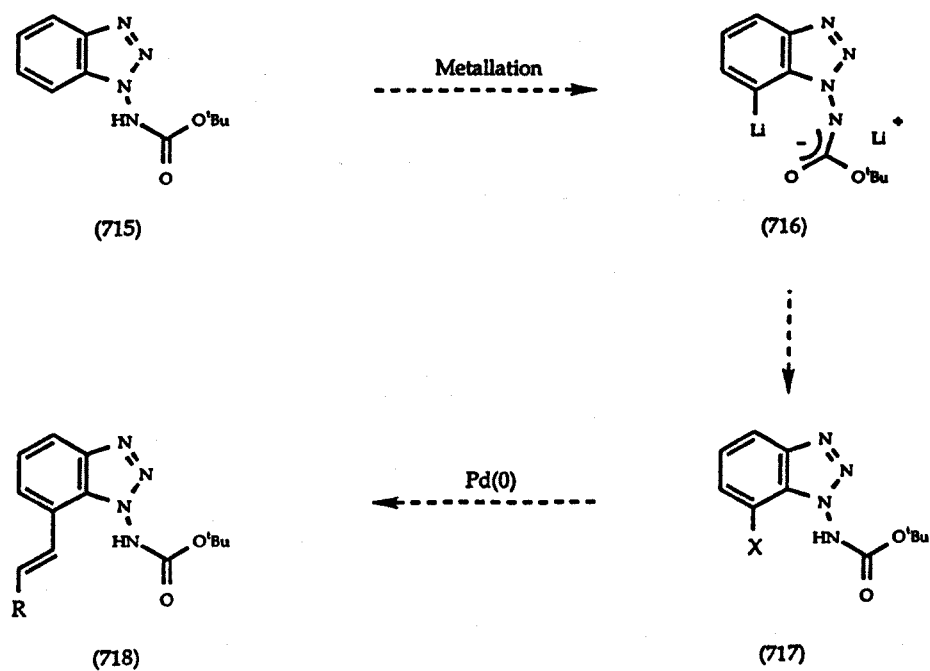


Scheme 261

The BOC-directed Metallation and Functionalisation of Aromatic sp^2 Centres

Although there appear to be relatively few examples of directed metallation of sp^3 centres by BOC groups, the directed lithiation and functionalisation of aromatic sp^2 centres has received a greater amount of attention.^{216, 266} On this basis, the action of organolithium bases on BOC-protected 1-aminobenzotriazole itself could result in the lithiation of the aromatic ring adjacent to the BOC group. The resulting dianionic intermediate (716) could then be used as an alternative route to dihydrobenzofurans and chromans. The stannylation of the dianionic intermediate ($X = \text{SnBu}_3$) could also yield a product suitable for Stille-type palladium(0)-catalysed couplings, whilst hydroxylation ($X = \text{OH}$) followed by

conversion to a triflate group ($X = \text{OTf}$) or halogenation ($X = \text{Br}, \text{I}$) could also generate similar precursors (*Scheme 262*).



Scheme 262

CHAPTER SEVEN

Experimental Section

- a) *General Details*
- b) *Preparation and Functionalisation of BOC-Protected 7-Methyl-1-Aminobenzotriazole*
- c) *Preparation of Chiral, Non-Racemic Lactaldehydes*
- d) *Deprotection of Functionalised 1-Aminobenzotriazoles*
- e) *Reactions of ortho-Substituted 1-Aminobenzotriazoles with N-Bromosuccinimide [NBS]*
- f) *Reactions of ortho-Substituted 1-Aminobenzotriazoles with Lead(IV) Acetate*
- g) *Reactions of ortho-Substituted 1-Aminobenzotriazoles with N-Iodosuccinimide [NIS]*
- h) *Coupling Reactions of Iodo-Dihydrobenzofurans and Iodo-Chromans*
- i) *Reactions of 1-Aminobenzotriazole with N-Iodosuccinimide [NIS]*

a) General Details

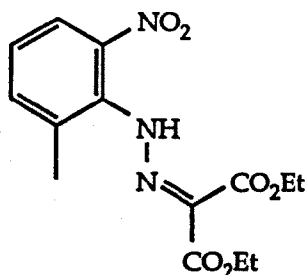
Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin Elmer 1720 FTIR as chloroform solutions. ^1H NMR spectra were recorded on Bruker WM 250 (250 MHz, PFT), Bruker AM 400 (400 MHz, PFT) and JEOL EX270 (270 MHz, PFT) instruments. The following abbreviations are used; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, br s = broad singlet *etc.* J values are given in Hz. ^{13}C NMR spectra were recorded on JEOL EX270 (68 MHz, PFT) and Bruker AM 400 (101 MHz, PFT) instruments. Chemical shifts (δ_{H} and δ_{C}) are reported in parts per million (ppm) from tetramethylsilane (or chloroform), and are corrected to 0.00 (TMS) and 7.27 (CHCl_3) ppm for ^1H NMR, and 77.30 (CDCl_3) ppm for ^{13}C NMR. Deuteriochloroform was used as solvent for NMR measurements. Where no clear resonances for the OH function of alcohols were observed, the values have not been quoted. Mass spectra and molecular weights were determined using either a VG MM707OE or AEI MS 902 spectrometer. Molecular formulae quoted for molecular fragment ions are converted to 3mmu. Optical rotations $[\alpha]_{\text{D}}$ were measured on a Jasco DIP 370 polarimeter. All reactions using air/moisture sensitive reagents were performed in oven-dried or flame-dried apparatus, under a nitrogen atmosphere. All solvents and reagents were purified according to procedures laid down in 'Purification of Laboratory Chemicals', by D. D. Perrin and W. L. F. Armarego. 'Petrol' refers to light petroleum, b.p. 40-60°C. All organic solutions were dried by brief exposure to anhydrous magnesium sulphate. Chromatography was performed using silica gel SORBSIL® (40-60 μm).

At this point, the author wishes to strongly emphasise to the reader

that due to the preliminary nature of the studies detailed in Chapter Six, most of the reported reactions were performed on small scales, and, consequently, quoted yields in most cases are unoptimised values. Additionally, because of the lack of material in most cases, the majority of compounds presented in this section do not possess microanalytical data. Therefore, structural elucidation in most cases has been accomplished by comparison of ^1H NMR, ^{13}C NMR and Mass Spectral data. For the readers attention, ^{13}C NMR spectra of some of the compounds lacking microanalytical data have been included, in an Appendix situated at the end of this thesis.

b) Preparation and Functionalisation of BOC-Protected 7-Methyl-1-Aminobenzotriazole (569)

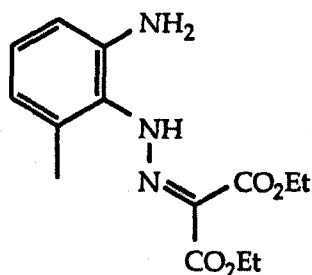
Diethyl 2-((2'-nitro-6'-methylphenyl)hydrazono)propanedioate (540)



To a three-necked round bottom flask containing concentrated hydrochloric acid (10M, 100 mL) at ambient temperature was added portionwise 2-methyl-6-nitroaniline (539) (52.15 g, 0.343 mol, 1 equivalent) over a period of 0.5h, with stirring being allowed to continue for a further 0.5h after addition was complete. Deionized water (200 mL) was then added, with the resulting suspension being cooled to 0°C prior to the dropwise addition of a solution of sodium nitrite (26.85 g, 0.377 mol, 1.1 equivalents) in deionized water (50 mL) over a period of 1h. The resulting solution was filtered, and the filtrate added dropwise over a period of 1h to a vigorously stirred emulsion of diethyl malonate (54.95 g, 0.343 mol, 1 equivalent) in deionized water (200 mL) at 5°C. Anhydrous sodium acetate (100 g) was added portionwise during the addition of the solution, and stirring was allowed to continue for a further period of 1h once addition of the solution was complete. The resulting orange-red suspension was filtered, and the solid recrystallized from methanol to yield the title compound (540) (54.71 g, 49%) as an amorphous orange powder, m.p. 64-65°C (lit.^{102a} 70°C); δ_{H} (250 MHz) 1.56 (3H, t, J 7.7,

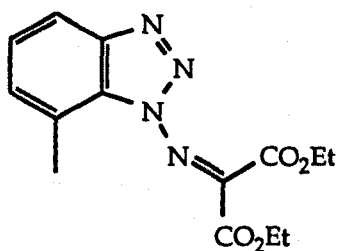
CH₂CH₃), 1.65 (3H, t, *J* 7.7, CH₂CH₃), 2.83 (3H, s, 6'-CH₃), 4.55 (2H, q, *J* 7.1, CH₂CH₃), 4.66 (2H, q, *J* 7.1, CH₂CH₃), 7.10 (1H, dd, *J* 7.6, 7.6, 4'-H), 7.48 (1H, dd, *J* 7.6, 1.0, 3'-H), 7.80 (1H, dd, *J* 7.6, 1.0, 5'-H) and 15.10 (1H, br s, NH).

Diethyl 2-((2'-amino-6'-methylphenyl)hydrazono)propanedioate (541)



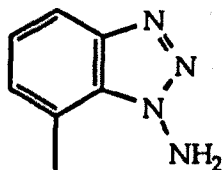
To a suspension of 10% palladium on charcoal (0.5 g) in ethanol (75 mL) at ambient temperature was added portionwise the iminomalonate (540) (10.0 g, 0.031 mol, 1 equivalent) and cyclohexene (15.26 g, 0.186 mol, 6 equivalents). The mixture was refluxed for 1.75h, then allowed to cool to ambient temperature before being filtered through Celite, with the filter cake being washed with further portions of ethanol (2 x 50 mL). The combined filtrates were cooled to 0°C, and the resulting suspension filtered to give the title compound (541) (5.51 g, 61%) as orange crystals, m.p. 103-104°C (lit.^{102a} 100-101°C); δ_{H} (250 MHz) 1.59 (3H, t, *J* 7.1, CH₂CH₃), 1.66 (3H, t, *J* 7.1, CH₂CH₃), 2.60 (3H, s, 6'-CH₃), 4.33 (2H, q, *J* 7.1, CH₂CH₃), 4.43 (2H, q, *J* 7.1, CH₂CH₃), 5.57 (2H, br s, NH₂), 6.52 (1H, dd, *J* 7.8, 1.0, 5'-H), 6.61 (1H, dd, *J* 7.8, 1.0, 3'-H), 6.82 (1H, dd, *J* 7.8, 7.8, 4'-H) and 13.54 (1H, br s, NH).

Diethyl 2-(7'-methyl-1H-benzotriazol-1'-iminyl)propanedioate (542)



To a suspension of the aniline (541) (5.51 g, 0.019 mol, 1 equivalent) in methanol (25 mL) at ambient temperature was added a solution of sodium nitrite (1.43 g, 0.021 mol, 1.1 equivalents) in deionized water (6 mL), and the resulting suspension added to a stirred ice-cold solution of concentrated hydrochloric acid (10M, 6 mL) in water (12 mL). The resulting solid was filtered off and recrystallized from aqueous methanol to give the title compound (542) (4.43 g, 77%) as an amorphous, light yellow powder, m.p. 67-68°C (lit.^{102a} 64-65°C), δ_H (250 MHz) 1.41 (6H, t, J 7.1, 2 \times CH₂CH₃), 2.78 (3H, s, 7'-CH₃), 4.50 (2H, q, J 7.1, CH₂CH₃), 4.55 (2H, q, J 7.1, CH₂CH₃), 7.33-7.36 (2H, m, 5'- & 6'-H) and 7.87 (1H, dd, J 7.1, 1.0, 4'-H).

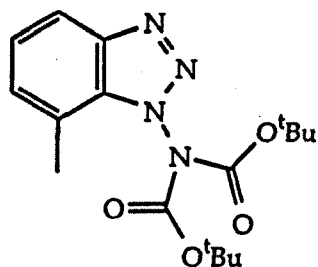
7-Methyl-1H-benzotriazol-1-amine (543)



To a stirred solution of the benzotriazole malonate (542) (8.52 g, 0.028 mol, 1 equivalent) in methanol (200 mL) maintained at 50°C was added

concentrated hydrochloric acid (10M, 50 mL). After stirring at this temperature for 3.5h, the solvent was removed under reduced pressure and the residue taken up into 2M hydrochloric acid (300 mL). The resulting solution was washed with diethyl ether (3 x 20 mL), neutralized with solid sodium carbonate and extracted with diethyl ether (3 x 150 mL). The combined organic extracts were dried and evaporated to yield a dark brown residue which was recrystallized from toluene to yield the title compound (543) (3.45 g, 83%) as an amorphous, colourless powder, m.p. 116-118°C (lit.^{102a} 116-118°C), δ_{H} (250 MHz) 2.90 (3H, s, 7-CH₃), 5.88 (2H, br s, NH₂), 7.32-7.38 (2H, m, 5- & 6-H) and 7.87-7.93 (1H, m, 4-H).

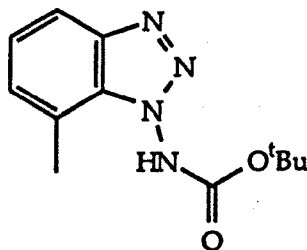
7-Methyl-1H-benzotriazol-1-(N,N-bis-tert-butoxycarbonyl)amine (568)



To a solution of the aminobenzotriazole (543) (1.00 g, 6.76 mmol, 1 equivalent), triethylamine (1.50 g, 15 mmol, 2.2 equivalents) and 4-dimethylaminopyridine (50 mg) in dichloromethane (40 mL) maintained at 0°C, was added dropwise *via* syringe a solution of di-*tert*-butyl dicarbonate (3.24 g, 15 mmol, 2.2 equivalents) in dichloromethane (1 mL). Following stirring for 48h at ambient temperature, the mixture was poured onto saturated aqueous sodium hydrogencarbonate (10 mL), and the separated organic layer washed with deionized water (10 mL) and brine (10 mL). Evaporation of the dried organic phase afforded a brown gum which was recrystallized from hexane/ethyl acetate (1:1) to give the

title compound (568) (2.10 g, 89%) as an amorphous, colourless powder, m.p. 113-115°C, ν_{\max} 2933, 1806, 1774, 1613, 1458, 1145, 1125, 996, 862 and 842 cm^{-1} , δ_{H} (250 MHz) 1.38 (18H, s, 2 x C(CH₃)₃), 2.49 (3H, s, 7-CH₃), 7.23-7.27 (2H, m, 5- & 6-H) and 7.85-7.89 (1H, m, 4-H), δ_{C} (68 MHz) 15.92 (CH₃), 27.64 (C(CH₃)₃), 85.75 (C(CH₃)₃), 118.17 (CH), 119.91 (C), 124.67 (CH), 129.70 (CH), 130.93 (C), 144.37 (C) and 148.70 (C=O), m/z [FAB] 349 (7%, M⁺ + H), 249 (7) and 149 (100). [Found: C, 58.5; H, 7.2; N, 16.0. C₁₇H₂₄N₄O₄ requires C, 58.6; H, 7.0; N, 16.1%].

7-Methyl-1H-benzotriazol-1-(N-tert-butoxycarbonyl)amine (569)



To a stirred solution of the *bis*-BOC aminobenzotriazole (568) (2.21 g, 6.34 mmol, 1 equivalent) in methanol (40 mL) maintained at 50°C, was added 2M sodium hydroxide (5mL). After stirring at this temperature for 40 min, the solvent was removed under reduced pressure to yield a brown residue, which was taken up in dichloromethane (50 mL), and washed with deionized water (20 mL) and brine (20 mL), then dried and evaporated to yield a yellow solid. Chromatography of this residue using petrol/ethyl acetate (3:1) as the eluant gave the *title compound* (569) (1.47 g, 98%) as a pale yellow oil which solidified upon high vacuum drying to give an amorphous, colourless powder, m.p. 105-106°C, ν_{\max} 3404, 2931, 1755, 1611, 1457, 1155, 1117, 1064, 1014, 907 and 867 cm^{-1} , δ_{H} (250 MHz) 1.45

(9H, br s, C(CH₃)₃), 2.62 (3H, s, 7-CH₃), 7.22-7.30 (2H, m, 4- & 6-H), 7.82-7.87 (1H, m, 5-H) and 8.35 (1H, s, NH), δ_C (68 MHz) 16.05 (CH₃), 27.91 (C(CH₃)₃), 83.40 (C(CH₃)₃), 117.56 (CH), 120.88 (C), 124.56 (CH), 129.51 (CH), 131.30 (C), 144.28 (C) and 153.69 (C=O), *m/z* [FAB] 249 (100%, M⁺ + H), 149 (95) and 134 (47). [Found: C, 58.2; H, 6.7; N, 22.8. C₁₂H₁₆N₄O₂ requires C, 58.1; H, 6.5; N, 22.6%].

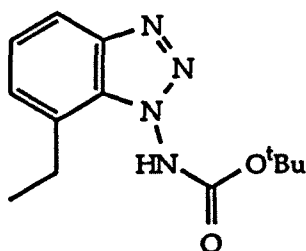
Metallation and Functionalisation of 7-Methyl-1H-benzotriazol-1-(N-tert-butoxycarbonyl)amine (569)

General Procedure:-

n-Butyllithium (1.6M solution in hexanes, 2.2 equivalents) was added dropwise to a stirred solution of dry, distilled N,N,N',N'-tetramethylethylenediamine [TMEDA] (2.2 equivalents) in dry tetrahydrofuran (10mL mmol⁻¹) maintained at -78°C (acetone/solid CO₂). Stirring was continued for 0.25h, after which a solution of the aminobenzotriazole (569) (1 equivalent) in dry tetrahydrofuran (1 mL mmol⁻¹) was added dropwise *via* syringe. The resulting burgundy red dianion solution was stirred for 5 minutes at -78°C, allowed to warm gradually to 0°C and maintained at this temperature for 0.5h, then re-cooled to -78°C before the rapid addition of a solution of the electrophile (1.1 equivalents) in dry tetrahydrofuran (1 mL mmol⁻¹). Unless otherwise stated, the reaction was allowed to stir at -78°C for 1h, upon which a solution of saturated aqueous ammonium chloride (10 mL) was added, the cooling bath removed and the reaction allowed to warm gradually to ambient temperature. The aqueous layer was acidified with 2M hydrochloric acid and extracted with diethyl ether (3 x 30 mL), with the combined organic extracts dried and evaporated to give a crude material

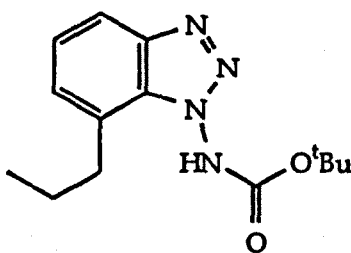
which was subjected to chromatography using petrol/ethyl acetate (3:1) to obtain the purified product.

7-Ethyl-1H-benzotriazol-1-(N-tert-butoxycarbonyl)amine (571)



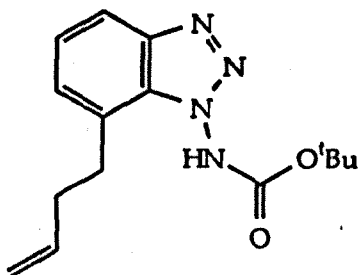
Following the general procedure, treatment of the dianion (570) generated from the aminobenzotriazole (569) (50 mg, 0.2 mmol) with dry, freshly distilled iodomethane (0.014 mL, 0.22 mmol) yielded the *title compound* (571) (50 mg, 95%) as a colourless gum, ν_{\max} 3399, 3220, 2934, 2854, 1756, 1608, 1461, 1154, 1118, 1080, 1003, 903 and 866 cm^{-1} , δ_{H} (250 MHz) 1.32 (3H, t, J 7.5, 2'-CH₃), 1.51 (9H, br s, C(CH₃)₃), 3.07 (2H, q, J 7.5, 1'-CH₂), 7.29-7.32 (2H, m, 5- & 6-H), 7.86-7.89 (1H, m, 4-H) and 8.27 (1H, s, NH), δ_{C} (101 MHz) 14.96 (CH₃), 23.12 (CH₂), 28.10 (C(CH₃)₃), 83.89 (C(CH₃)₃), 118.04 (CH), 124.86 (C), 127.41 (CH), 127.98 (CH), 130.85 (C), 144.86 (C) and 153.48 (C=O), m/z [EI] 262 (6%, M⁺), 189 (25), 178 (20), 119 (12), 118 (18), 105 (22), 91 (14) and 77 (14). [Found: M⁺, 262.1405. C₁₃H₁₈N₄O₂ requires M, 262.1429].

7-Propyl-1H-benzotriazol-1-(N-tert-butoxycarbonyl)amine (574)



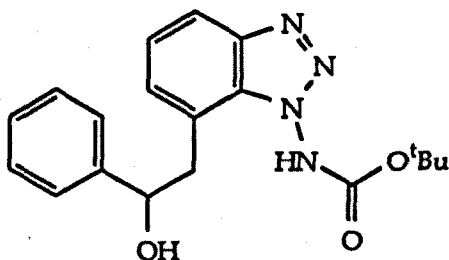
By the general procedure, treatment of the dianion (570) generated from the aminobenzotriazole (569) (50 mg, 0.2 mmol) with dry, distilled iodoethane (0.018 mL, 0.22 mmol) yielded the *title compound* (574) (50 mg, 90%) as a colourless gum, ν_{\max} 3397, 3228, 2931, 2855, 1756, 1608, 1458, 1154, 1121, 1090, 1004 and 906 cm^{-1} , δ_{H} (250 MHz) 0.97 (3H, t, J 7.5, 3'-CH₃), 1.51 (9H, br s, C(CH₃)₃), 1.60-1.80 (2H, m, 2'-CH₂), 2.95 (2H, t, J 7.5, 1'-CH₂), 7.27-7.33 (2H, m, 5- & 6-H), 7.85-7.89 (1H, m, 4-H) and 8.26 (1H, s, NH), δ_{C} (101 MHz) 14.08 (CH₃), 24.20 (CH₂), 28.10 (C(CH₃)₃), 32.31 (CH₂), 83.88 (C(CH₃)₃), 118.10 (CH), 124.71 (CH), 125.71 (C), 128.98 (CH), 131.20 (C), 144.92 (C) and 153.43 (C=O), m/z [EI] 276 (5%, M⁺), 203 (10), 192 (6), 163 (7), 151 (13), 113 (8) and 91 (12). [Found: M⁺, 276.1615. C₁₄H₂₀N₄O₂ requires M, 276.1586].

7-(But-3'-enyl)-1H-benzotriazol-1-(N-tert-butoxycarbonyl)amine (575)



Using the general procedure, treatment of the dianion (570) generated from aminobenzotriazole (569) (124 mg, 0.5 mmol) with dry, distilled allyl bromide (67 mg, 0.55 mmol) yielded the *title compound* (575) (122 mg, 85%) as an amorphous, colourless powder m.p. 87-88°C, ν_{\max} 3395, 3218, 2989, 2932, 2859, 1756, 1640, 1610, 1457, 1153, 1098, 994, 912 and 867 cm^{-1} , δ_{H} (400 MHz) 1.49 (9H, br s, $\text{C}(\text{CH}_3)_3$), 2.45 (2H, dt, J 8.2, 3.6, 2'- CH_2), 3.06 (2H, t, J 8.2, 1'- CH_2), 5.00-5.08 (2H, m, 4'- CH_2), 5.81-5.91 (1H, m, 3'-CH), 7.21-7.30 (2H, m, 5- & 6-H), 7.83-7.88 (1H, m, 4-H) and 8.69 (1H, s, NH), δ_{C} (101 MHz) 28.10 ($\text{C}(\text{CH}_3)_3$), 29.56 (CH_2), 34.73 (CH_2), 83.82 ($\text{C}(\text{CH}_3)_3$), 115.64 (CH_2), 118.18 (CH), 124.70 (CH), 125.11 (C), 128.90 (CH), 131.02 (C), 137.30 (CH), 144.92 (C) and 153.43 (C=O), m/z [FAB] 289 (61%, $\text{M}^+ + \text{H}$) and 189 (6). [Found: $\text{M}^+ + \text{H}$, 289.1674. $\text{C}_{15}\text{H}_{21}\text{N}_4\text{O}_2$ requires $\text{M} + \text{H}$, 289.1664].

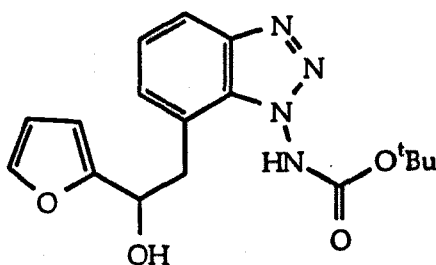
7-(2'-Hydroxy-2'-phenyl)ethyl-1H-benzotriazol-1-(N-tert-butoxy-carbonyl)amine (635)



Following the general procedure, the dianion (570) generated from aminobenzotriazole (569) (124 mg, 0.5 mmol) was treated with dry, freshly distilled benzaldehyde (59 mg, 0.55 mmol) to yield the *title compound* (635) (150 mg, 85%) as a colourless gum, ν_{\max} 3270, 2990, 2933, 1754, 1606, 1492, 1456, 1153, 1115, 910 and 638 cm^{-1} , δ_{H} (400 MHz) 1.48 (9H, br s,

C(CH₃)₃), 3.20 (1H, dd, *J*_{AB} 11.5, 1.0, 1'-CH_{2A}), 3.28 (1H, dd, *J*_{AB} 14.4, 9.1, 1'-CH_{2B}), 4.90 (1H, dd, *J* 8.5, 3.5, 2'-CH), 7.21-7.38 (7H, m, 5-, 6-H & ArH), 7.74 (1H, dd, *J* 7.3, 1.9, 4-H) and 9.49 (1H, s, NH), δ_c (68 MHz) 28.14 (C(CH₃)₃), 40.27 (CH₂), 75.29 (CH), 83.57 (C(CH₃)₃), 118.75 (CH), 121.64 (C), 124.68 (CH), 125.72 (CH), 128.05 (CH), 128.60 (CH), 130.42 (CH), 131.25 (C), 143.74 (C), 144.92 (C) and 154.12 (C=O), *m/z* [FAB] 355 (80%, M⁺ + H), 337 (8), 298 (85), 282 (20), 255 (20) and 238 (15). [Found: M⁺ + H, 355.1741. C₁₉H₂₃N₄O₃ requires M + H, 355.1770].

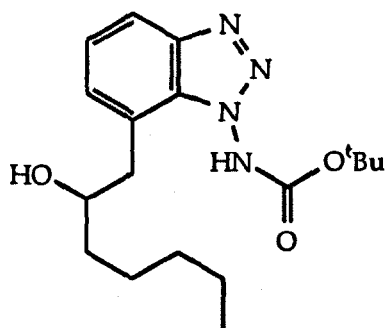
7-(2'-Furanyl-2'-hydroxy)ethyl-1H-benzotriazol-1-(N-tert-butoxycarbonyl)amine (636)



Using the general procedure, the dianion (570) generated from the aminobenzotriazole (569) (124 mg, 0.5 mmol) was treated with dry, freshly distilled 2-furaldehyde (53 mg, 0.55 mmol) to yield the *title compound* (636) (139 mg, 81%) as a colourless gum, ν_{\max} 3592, 3308, 2936, 1754, 1608, 1487, 1457, 1153, 1115, 1006, 911 and 862 cm⁻¹; δ_H (250 MHz) 1.40 (9H, br s, C(CH₃)₃), 3.29-3.39 (2H, m, 1'-CH₂), 4.50-4.97 (1H, m, 2'-CH), 6.11-6.30 (2H, m, 3'' & 4''-H), 7.13-7.32 (3H, m, 5, 6-H and 5''-H), 7.63-7.80 (1H, m, 4-H) and 9.08 (1H, s, NH), δ_c (101 MHz) 28.12 (C(CH₃)₃), 36.29 (CH₂), 68.57 (CH), 83.57 (C(CH₃)₃), 106.37 (CH), 110.46 (CH), 119.01 (CH), 121.02 (C), 124.70 (CH), 130.41 (CH), 131.26 (C), 142.15 (CH), 144.78 (C), 154.12 (C=O) and 155.67 (C), *m/z* [FAB] 345 (70%, M⁺ + H), 327 (21), 288 (100), 272 (32) and

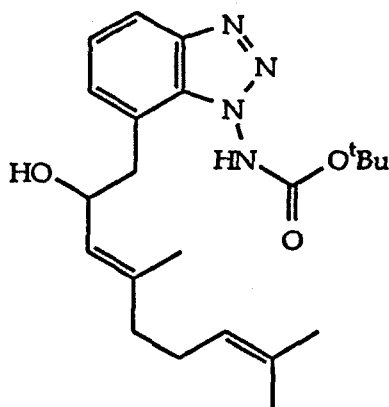
245 (41). [Found: $M^+ + H$, 345.1614. $C_{17}H_{21}N_4O_4$ requires $M + H$, 345.1562].

7-(2'-Hydroxyheptyl)-1H-benzotriazol-1-(N-tert-butoxycarbonyl)amine
(637)



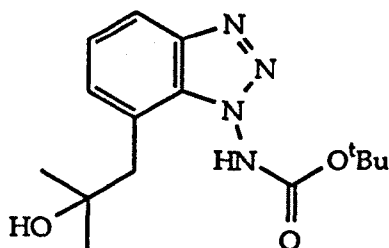
Following the general procedure, the dianion (570) generated from aminobenzotriazole (569) (124 mg, 0.5 mmol) was treated with dry, freshly distilled *n*-hexanal (53 mg, 0.55 mmol) and stirring allowed to continue at -78°C for 3h before giving the *title compound* (637) (96 mg, 55%) as a colourless gum, ν_{max} 3262, 2930, 2858, 1754, 1458, 1156 1156, 1118, 994, 908 and 862 cm^{-1} , δ_{H} (250 MHz) 0.91 (3H, t, J 6.6, 7'-CH₃), 1.16-1.62 (8H, m, 3'-, 4'-, 5'- & 6'-CH₂), 1.51 (9H, br s, C(CH₃)₃), 2.96-3.04 (2H, m, 1'-CH₂), 3.80-3.95 (1H, m, 2'-CH), 7.25-7.32 (2H, m, 5- & 6-H), 7.86 (1H, dd, J 7.6, 1.6, 4-H) and 9.27 (1H, s, NH), δ_{C} (101 MHz) 14.02 (CH₃), 22.55 (CH₂), 25.12 (CH₂), 28.07 (C(CH₃)₃), 31.79 (CH₂), 37.41 (CH₂), 37.49 (CH₂), 72.58 (CH), 83.24 (C(CH₃)₃), 118.31 (CH), 122.12 (C), 124.58 (CH), 130.01 (CH), 131.08 (C), 144.42 (C), and 154.14 (C=O), m/z [FAB] 349 (100%, $M^+ + H$), 293 (93), 273 (20) and 249 (17). [Found: $M^+ + H$, 349.2234. $C_{18}H_{29}N_4O_3$ requires $M + H$, 349.2240].

7-(4',8'-Dimethyl-2'-hydroxy-(E,E)-nonadien-3',7'-yl)-1H-benzotriazol-1-(N-tert-butoxycarbonyl)amine (638)



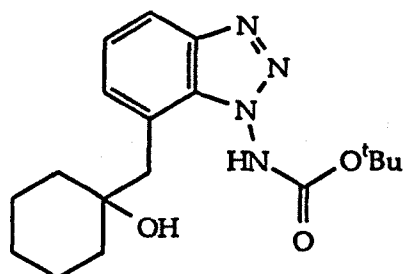
Following the general procedure, treatment of the dianion (570) generated from aminobenzotriazole (569) (124 mg, 0.5 mmol) with dry, freshly distilled citral (53 mg, 0.55 mmol) and stirring for 3h at -78°C furnished the *title compound* (638) (106 mg, 53%) as a colourless gum, ν_{max} 3270, 2990, 2933, 1750, 1606, 1492, 1456, 1155, 1153, 910 and 890 cm^{-1} , δ_{H} (250 MHz) 1.52 (9H, br s, $\text{C}(\text{CH}_3)_3$), 1.60 (3H, s, 4'- CH_3), 1.65 (3H, s, 8'- CH_3), 1.66 (3H, s, 8'- CH_3), 2.02-2.17 (4H, m, 5'- & 6'- CH_2), 3.08-3.11 (2H, m, 1'- CH_2), 4.60-4.80 (1H, m, 2'-CH), 5.08-5.25 (2H, m, 3'- & 7'-CH), 7.24-7.33 (2H, m, 5- & 6-H), 7.88 (1H, dd, J 7.6, 1.3, 4-H) and 9.39 (1H, s, NH), δ_{C} (101 MHz) 16.71 (CH_3), 17.77 (CH_3), 25.71 (CH_2), 25.75 (CH_3), 26.37 (CH), 28.20 ($\text{C}(\text{CH}_3)_3$), 37.60 (CH_2), 39.56 (CH_2), 68.57 (CH), 83.57 ($\text{C}(\text{CH}_3)_3$), 118.78 (CH), 121.30 (C), 123.72 (CH), 124.48 (CH), 126.27 (CH), 130.43 (CH), 131.38 (C), 132.03 (C), 139.46 (C), 144.81 (C) and 154.12 ($\text{C}=\text{O}$), m/z [FAB] 401 (18%, $\text{M}^+ + \text{H}$), 383 (5), 345 (11), 327 (12) and 301 (5). [Found: $\text{M}^+ + \text{H}$, 401.2549. $\text{C}_{23}\text{H}_{25}\text{N}_4\text{O}_3$ requires $\text{M} + \text{H}$, 401.2553].

7-(2'-Hydroxy-2'-methyl)propyl-1H-benzotriazol-1-(N-tert-butoxy-carbonyl)amine (639)



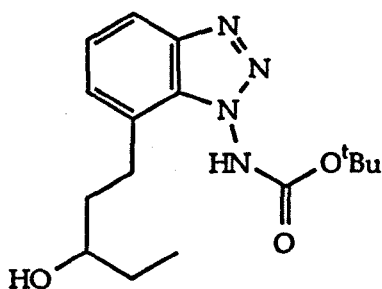
Following the general procedure, treatment of the dianion (570) generated from the aminobenzotriazole (569) (108 mg, 0.44 mmol) with dry, freshly distilled acetone (28 mg, 0.48 mmol), followed by further stirring at -78°C for 3h furnished the *title compound* (639) (93 mg, 70%) as an amorphous, colourless powder, m.p. $162\text{--}163^{\circ}\text{C}$, ν_{max} 3208, 2993, 2991, 2860, 1755, 1609, 1490, 1458, 1116, 964, 900, 868, 837 and 644 cm^{-1} , δ_{H} (250 MHz) 1.35 (6H, s, $2 \times \text{CH}_3$), 1.52 (9H, br s, $\text{C}(\text{CH}_3)_3$), 2.98 (2H, s, $1'\text{-CH}_2$), 3.27 (1H, br s, OH), 7.17 (1H, dd, J 7.6, 1.0, 6-H), 7.28 (1H, dd, J 7.6, 7.6, 5-H), 7.75 (1H, dd, J 7.6, 1.0, 4-H) and 9.61 (1H, br s, NH), δ_{C} (101 MHz) 28.17 ($\text{C}(\text{CH}_3)_3$), 29.67 ($2 \times \text{CH}_3$), 42.98 (CH_2), 71.28 (C), 83.02 ($\text{C}(\text{CH}_3)_3$), 118.65 (CH), 120.71 (C), 124.33 (CH), 131.21 (CH), 131.29 (C), 144.38 (C), and 154.64 (C=O), m/z [FAB] 307 (100%, $\text{M}^+ + \text{H}$), 251 (55), 233 (10) and 207 (14). [Found: $\text{M}^+ + \text{H}$, 307.1778. $\text{C}_{15}\text{H}_{23}\text{N}_4\text{O}_3$ requires $\text{M} + \text{H}$, 307.1770].

7-(2'-Hydroxycyclohexylmethylene)-1H-benzotriazol-1-(N-tert-butoxy-carbonyl)amine (640)



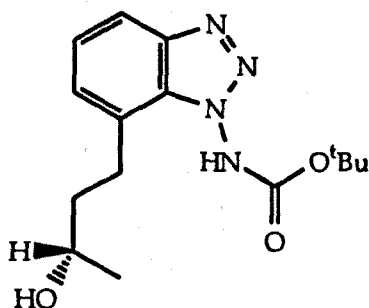
Using the general procedure, treatment of the dianion (570) generated from the aminobenzotriazole (569) (124 mg, 0.5 mmol) with dry, freshly distilled cyclohexanone (54 mg, 0.55 mmol) followed by stirring at -78°C for 3h gave the *title compound* (640) (107 mg, 62%) as an amorphous, colourless powder, m.p. $152\text{--}154^{\circ}\text{C}$, ν_{max} 3252, 2934, 2856, 1754, 1457, 1156, 971 and 912 cm^{-1} , δ_{H} (250 MHz) 1.51 (9H, br s, $\text{C}(\text{CH}_3)_3$), 1.11–1.60 (10H, m, $5 \times \text{CH}_2$), 2.81 (1H, br s, OH), 2.99 (2H, s, $1'\text{-CH}_2$), 7.18 (1H, dd, J 8.0, 1.0, 6-H), 7.27 (1H, dd, J 8.0, 8.0, 5-H), 7.77 (1H, dd, J 8.0, 1.0, 4-H) and 9.61 (1H, br s, NH), δ_{C} (101 MHz) 21.91 ($2 \times \text{CH}_2$), 25.52 ($2 \times \text{CH}_2$), 28.11 ($\text{C}(\text{CH}_3)_3$), 37.54 (CH_2), 42.05 (CH_2), 72.00 (C), 82.93 ($\text{C}(\text{CH}_3)_3$), 118.20 (CH), 120.09 (C), 124.15 (CH), 131.09 (CH), 131.14 (C), 144.42 (C) and 154.14 (C=O), m/z [FAB] 347 (86%, $\text{M}^+ + \text{H}$), 291 (55) and 247 (17). [Found: C, 62.4; H, 7.7; N, 15.9. $\text{C}_{18}\text{H}_{26}\text{N}_4\text{O}_3$ requires C, 62.4; H, 7.6; N, 16.1%: $\text{M}^+ + \text{H}$, 347.2096. $\text{C}_{18}\text{H}_{27}\text{N}_4\text{O}_3$ requires M + H, 347.2083].

7-(3'-Hydroxypentyl)-1H-benzotriazol-1-(N-tert-butoxycarbonyl)amine
(658)



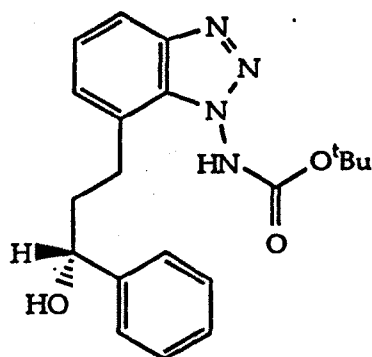
Using the general procedure, treatment of the dianion (570) generated from the aminobenzotriazole (569) (124 mg, 0.5 mmol) with dry, freshly distilled 1,2-epoxybutane (40 mg, 0.55 mmol) followed by stirring at -60°C for 3h yielded the *title compound* (658) (140 mg, 88%) as a colourless gum, ν_{max} 3285, 2934, 2856, 1754, 1458, 1156, 984 and 912 cm^{-1} , δ_{H} (270 MHz) 0.91 (3H, t, J 7.4, 5'-CH₃), 1.46 (9H, br s, C(CH₃)₃), 1.71-1.90 (4H, m, 2'- & 4'-CH₂), 2.28 (1H, br s, OH), 3.10 (2H, m, 1'-CH₂), 3.35-3.50 (1H, m, 3'-CH), 7.23-7.32 (2H, m, 5- & 6-H), 7.83-7.89 (1H, m, 4-H) and 9.53 (1H, br s, NH), δ_{C} (68 MHz) 9.83 (CH₃), 25.64 (CH₂), 27.94 (C(CH₃)₃), 30.12 (CH₂), 38.04 (CH₂), 72.24 (CH), 82.27 (C(CH₃)₃), 117.75 (CH), 124.71 (CH), 125.46 (C), 128.77 (CH), 130.75 (C), 144.56 (C) and 154.07 (C=O), m/z [FAB] 321 (100%, $\text{M}^+ + \text{H}$), 265 (35), 247 (12) and 221 (16). [Found: $\text{M}^+ + \text{H}$, 321.1925. $\text{C}_{16}\text{H}_{25}\text{N}_4\text{O}_3$ requires $\text{M} + \text{H}$, 321.1927].

7-(3'-(S)-(-)-Hydroxybutyl)-1H-benzotriazol-1-(N-tert-butoxycarbonyl)-amine (681)



Following the general procedure, treatment of the dianion (570) generated from the aminobenzotriazole (569) (248 mg, 1 mmol) with dry, freshly distilled (S)-(-)-propylene oxide (64 mg, 1.1 mmol) was followed by allowing the mixture to gradually warm to ambient temperature after 5h stirring at -78°C . After stirring overnight, the *title compound* (681) (236 mg, 78%) was isolated as a colourless gum, $[\alpha]_D = -20.10$ [(c = 1.0, 25°C , CH_2Cl_2)], ν_{max} 3191, 2990, 2932, 2850, 1748, 1608, 1458, 1154, 1118, 1002, 949, 901 and 866 cm^{-1} , δ_{H} (250 MHz) 1.22 (3H, d, J 6.2, 4'- CH_3), 1.45 (9H, br s, $\text{C}(\text{CH}_3)_3$), 1.78-1.88 (2H, m, 2'- CH_2), 3.10 (2H, t, J 7.5, 1'- CH_2), 3.70-3.78 (1H, m, 3'-CH), 7.27-7.30 (2H, m, 5- & 6-H), 7.83-7.86 (1H, m, 4-H) and 9.51 (1H, br s, NH), δ_{C} (68 MHz) 23.70 (CH_3), 25.90 (CH_2), 28.10 ($\text{C}(\text{CH}_3)_3$), 40.44 (CH_2), 67.18 (CH), 83.60 ($\text{C}(\text{CH}_3)_3$), 118.09 (CH), 124.90 (CH), 125.40 (C), 129.03 (CH), 130.92 (C), 144.77 (C) and 154.05 (C=O), m/z [FAB] 307 (100%, $\text{M}^+ + \text{H}$), 251 (63), 233 (41) and 207 (60). [Found: $\text{M}^+ + \text{H}$, 307.1772. $\text{C}_{15}\text{H}_{23}\text{N}_4\text{O}_3$ requires $\text{M} + \text{H}$, 307.1770].

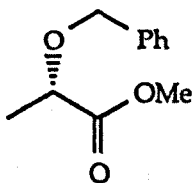
7-(3'-(R)-(+)-Hydroxy-3'-phenylpropyl)-1H-benzotriazol-1-(N-tert-butoxycarbonyl)amine (682)



Using the general procedure, treatment of the dianion (570) generated from the aminobenzotriazole (569) (248 mg, 1 mmol) with dry, freshly distilled (S)-(-)-styrene oxide (132 mg, 1.1 mmol) was followed by stirring at -78°C for 6h. After allowing to warm to ambient temperature overnight, the *title compound* (682) (129 mg, 44%) was isolated as a colourless gum, $[\alpha]_{\text{D}} = +27.0$ $[(c = 1.0, 25^{\circ}\text{C}, \text{CH}_2\text{Cl}_2)]$, ν_{max} 3191, 2990, 2934, 2852, 1751, 1608, 1456, 1155, 1111, 1009 and 908 cm^{-1} , δ_{H} (250 MHz) 1.43 (9H, br s, $\text{C}(\text{CH}_3)_3$), 2.01-2.06 (2H, m, 2'- CH_2), 3.05 (2H, t, J 6.9, 1'- CH_2), 4.55-4.65 (1H, m, 3'-CH), 7.22-7.35 (7H, m, 5-, 6-H & ArH), 7.76-7.80 (1H, m, 4-H) and 9.46 (1H, s, NH), δ_{C} (101 MHz) 25.99 (CH_2), 28.29 ($\text{C}(\text{CH}_3)_3$), 39.89 (CH_2), 73.46 (CH), 83.61 ($\text{C}(\text{CH}_3)_3$), 118.10 (CH), 124.91 (CH), 125.23 (C), 125.99 (CH), 127.78 (CH), 128.48 (CH), 128.61 (CH), 128.77 (CH), 128.97 (CH), 131.74 (C), 144.03 (C), 144.76 (C) and 154.77 ($\text{C}=\text{O}$) m/z [FAB] 369 (100%, $\text{M}^+ + \text{H}$), 313 (62), 295 (51) and 269 (35). [Found: $\text{M}^+ + \text{H}$, 369.1913. $\text{C}_{20}\text{H}_{25}\text{N}_4\text{O}_3$ requires $\text{M} + \text{H}$, 369.1927].

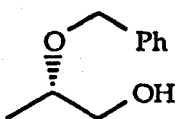
c) Preparation of Chiral, Non-Racemic Lactaldehydes

(S)-Methyl 2-Benzzyloxypropionate (668)



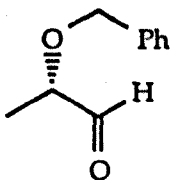
To a solution of sodium hydride (97 mg, 0.05 mol, 60% dispersion in mineral oil, 1.05 equivalents) in dry tetrahydrofuran (100 mL) at ambient temperature was added the methyl lactate (667) (5.00 g, 0.048 mol, 1 equivalent). The mixture was maintained at this temperature for 3h, then catalytic tetra-*n*-butyl ammonium iodide (50 mg) was added. Following stirring for a further 10 minutes, benzyl bromide (8.30 g, 0.053 mol, 1.1 equivalents) was added dropwise, and after allowing to stir at ambient temperature overnight, the mixture was partitioned between deionized water (20 mL) and diethyl ether (100 mL). The aqueous layer was extracted with further portions of diethyl ether (3 x 100 mL), and the combined organic extracts dried and evaporated under reduced pressure to yield a yellow oil, which was separated by chromatography using petrol/ethyl acetate (9:1) to furnish the title compound²⁵⁰ (668) (5.63 g, 65%) as a pale yellow oil, δ_{H} (250 MHz) 1.44 (3H, d, *J* 6.9, 3-CH₃), 3.76 (3H, s, CO₂CH₃), 4.07 (1H, q, *J* 6.9, 2-CH), 4.45 (1H, d, *J* 11.0, ArCH_{2A}), 4.68 (1H, d, *J* 11.0, ArCH_{2B}) and 7.31-7.37 (5H, m, ArH).

(S)-2-Benzylxypropan-1-ol (669)



To a solution of the methyl ester (668) (2.00 g, 0.011 mol, 1 equivalent) in dry toluene (30 mL) maintained at -78°C (acetone/solid CO_2) was added dropwise *via* syringe a solution of diisobutylaluminium hydride [DIBAL-H] in toluene (2.80 mL, 0.028 mmol, 1.0M solution in toluene, 2.5 equivalents). The mixture was allowed to warm gradually to ambient temperature overnight, then treated with saturated ammonium chloride solution (1 mL) and methanol (1mL). After allowing to stir for a further 0.5h, the resulting suspension was filtered through kieselguhr, and the residue washed with diethyl ether (2 x 100 mL). The combined filtrates were dried and evaporated to give a yellow oil, which was separated by chromatography using petrol/ethyl acetate (95:5) to yield the title compound²⁵⁰ (669) (0.71 g, 42%) as a colourless oil, δ_{H} (250 MHz) 1.22 (3H, d, J 6.9, 3- CH_3), 3.38-3.74 (3H, m, 1- CH_2 & 2-CH), 4.40 (1H, d, J 11.0, $\text{ArCH}_{2\text{A}}$), 4.64 (1H, d, J 11.0, $\text{ArCH}_{2\text{B}}$) and 7.18-7.38 (5H, m, ArH).

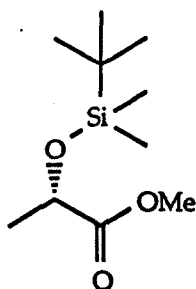
(S)-2-Benzylxypropanal (670)



To a solution of the lactyl alcohol (669) (1.00 g, 6.58 mmol, 1

equivalent) and 4-methylmorpholine-N-oxide (0.89 g, 7.57 mmol, 1.15 equivalents) in dry dichloromethane (50 mL) containing powdered 4Å molecular sieves (1.00 g) at ambient temperature was added catalytic tetra-*n*-propyl ammonium perruthenate (116 mg, 0.33 mmol, 5 mol %). The mixture was allowed to stir for 4h, then filtered through kieselguhr, with the filter cake being washed with further portions of dichloromethane (3 x 50 mL). The combined organic extracts were evaporated under reduced pressure to yield a yellow oil, which was separated by chromatography using petrol/ethyl acetate (95:5) to give the title compound²⁵⁰ (670) (0.64 g, 65%) as a colourless oil, δ_{H} (250 MHz) 1.18 (3H, d, *J* 6.9, 3-CH₃), 3.65 (1H, dd, *J* 6.9, 1.9, 2-CH), 4.56 (1H, s, ArCH₂), 7.26 (5H, s, ArH) and 9.56 (1H, d, *J* 1.9, 1-CH).

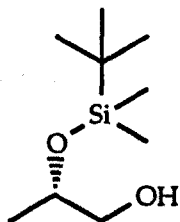
(S)-Methyl 2-(*tert*-Butyldimethylsilyloxy)propionate (671)



To a solution of *tert*-butyldimethylsilyl chloride (7.32 g, 0.053 mol, 1.1 equivalents) and imidazole (7.20 g, 0.11 mol, 2 equivalents) in dry dimethylformamide [DMF] (100 mL) at ambient temperature was added the methyl lactate (667) (5.00 g, 0.048 mol, 1 equivalent). The mixture was maintained at this temperature for 24h, then deionized water (150 mL) was added. The aqueous layer was extracted with petrol (3 x 100 mL), and the combined organic extracts dried and evaporated under reduced pressure to give a yellow oil, which was separated by column

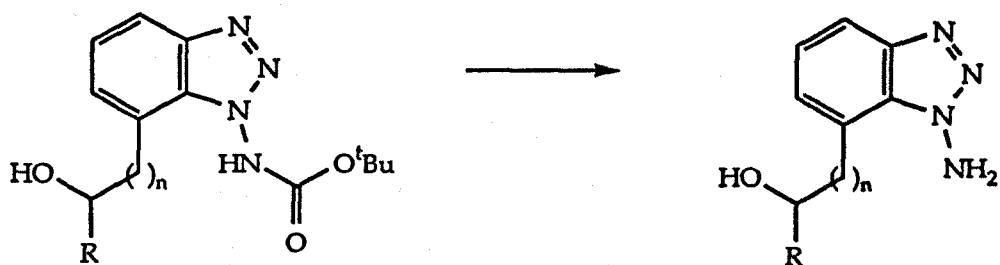
chromatography using petrol/ethyl acetate (95:5) to give the title compound²⁵⁰ (671) (9.41 g, 95%) as a colourless oil, δ_{H} (250 MHz) 0.06 (3H, s, SiCH₃), 0.08 (3H, s, SiCH₃), 0.88 (9H, s, SiC(CH₃)₃), 1.37 (3H, d, *J* 6.7, 3-CH₃), 3.70 (3H, s, CO₂CH₃) and 4.24 (1H, q, *J* 6.7, 2-CH).

(S)-2-(tert-Butyldimethylsilyloxy)propan-1-ol (672)



To a solution of the methyl ester (671) (2.00 g, 0.097 mmol, 1 equivalent) in dry toluene (30 mL) maintained at -78°C (acetone/solid CO₂) was added dropwise *via* syringe a solution of diisobutylaluminium hydride [DIBAL-H] in toluene (2.4 mL, 0.024 mol, 1.0M solution in toluene, 2.5 equivalents). The mixture was allowed to warm gradually to ambient temperature overnight, then treated with saturated ammonium chloride solution (1 mL) and methanol (1mL). After allowing to stir for a further 0.5h, the resulting suspension was filtered through kieselguhr, and the residue washed with diethyl ether (2 x 100 mL). The combined organic extracts were dried and evaporated to give a yellow oil which was separated by chromatography using petrol/ethyl acetate (95:5) to yield the title compound²⁵⁰ (672) (1.35 g, 73%) as a pale yellow oil, δ_{H} (250 MHz) 0.05 (3H, s, SiCH₃), 0.07 (3H, s, SiCH₃), 0.86 (9H, s, SiC(CH₃)₃), 1.37 (3H, d, *J* 6.7, 3-CH₃) and 3.20-3.70 (3H, m, 1-CH₂ & 2-CH).

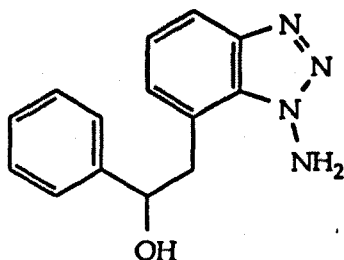
d) Deprotection of Functionalised 1-Aminobenzotriazoles



General Procedure:-

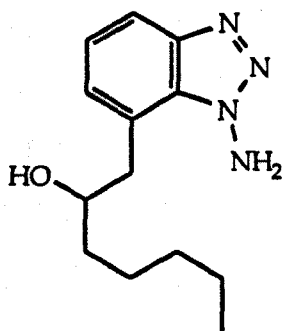
To a stirred solution of the functionalised aminobenzotriazole (1 equivalent) in dichloromethane (10 mL mmol^{-1}) under nitrogen at ambient temperature, was added dropwise *via* syringe trifluoroacetic acid [TFA] (20% *v/v* dichloromethane). After allowing to stir at this temperature for 0.5h, the solvent was removed under reduced pressure and the residue basified with aqueous 2M sodium hydroxide. The aqueous phase was extracted with diethyl ether ($3 \times 30 \text{ mL}$) and the combined organic extracts dried and evaporated to yield a crude residue which was subjected to chromatography using petrol/ethyl acetate (1:1) to obtain the purified product.

7-(2'-Hydroxy-2'-phenylethyl)-1H-benzotriazol-1-amine (641)



Following the general procedure above, treatment of the aminobenzotriazole (635) (75 mg, 0.2 mmol) with TFA furnished the *title compound* (641) (24 mg, 45%) as a colourless gum, ν_{\max} 3245, 2814, 1606, 1455, 1114, 910 and 644 cm^{-1} , δ_{H} (250 MHz) 1.59 (1H, br s, OH), 3.47-3.56 (2H, m, 1'-CH₂), 4.98 (1H, dd, *J* 8.0, 4.6, 2'-CH), 5.94 (2H, s, NH₂), 7.09 (1H, dd, *J* 7.8, 1.0, 6-H), 7.15 (1H, dd, *J* 7.8, 7.8, 5-H), 7.16-7.26 (5H, m, ArH) and 7.76 (1H, dd, *J* 7.8, 1.0, 4-H), δ_{C} (68 MHz) 40.25 (CH₂), 75.24 (CH), 118.47 (CH) 122.38 (C), 124.35 (CH), 125.81 (2 x CH), 127.93 (CH), 128.54 (2 x CH), 129.84 (CH), 130.89 (C), 143.77 (C) and 145.26 (C), *m/z* [FAB] 255 (100%, M⁺ + H), 237 (18) and 189 (21). [Found: M⁺ + H, 255.1263. C₁₄H₁₅N₄O requires M + H, 255.1246].

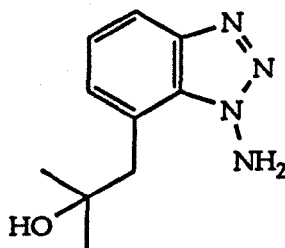
7-(2'-Hydroxyheptyl)-1H-benzotriazol-1-amine (642)



Following the general procedure, treatment of aminobenzotriazole (637) (164 mg, 0.47 mmol) with TFA furnished the *title compound* (642) (88 mg, 75%) as a colourless gum, ν_{\max} 3363, 2931, 2858, 1603, 1459, 1118 and 947 cm^{-1} , δ_{H} (250 MHz) 0.87-1.18 (3H, t, *J* 6.1, 7'-CH₃), 1.20-1.60 (8H, m, 3'-, 4'-, 5'- & 6'-CH₂), 3.20-3.29 (2H, m, 1'-CH₂), 3.90-3.94 (1H, m, 2'-CH), 6.21 (2H, s, NH₂), 7.18-7.22 (2H, m, 5- & 6-H) and 7.63-7.67 (1H, m, 4-H), δ_{C} (68 MHz) 14.02 (CH₃), 22.60 (CH₂), 25.38 (CH₂), 31.80 (CH₂), 37.23 (CH₂), 38.19

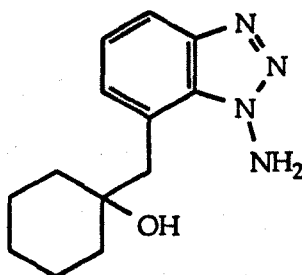
(CH₂), 72.58 (CH), 117.70 (CH), 123.25 (C), 124.21 (CH), 129.24 (CH), 131.27 (C) and 144.27 (C), *m/z* [FAB] 249 (100%, M⁺ + H), 234 (5), 148 (5) and 134 (3). [Found: M⁺ + H = 249.1721. C₁₃H₂₁N₄O requires M + H, 249.1715].

7-(2'-Hydroxy-2'-methylpropyl)-1H-benzotriazol-1-amine (644)



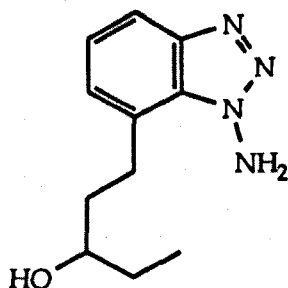
Following the general procedure, treatment of aminobenzotriazole (639) (53 mg, 0.17 mmol) with TFA gave the *title compound* (644) (28 mg, 78%) as a colourless gum, ν_{\max} 3348, 2928, 2855, 1719, 1457, 1092, 962 and 885 cm⁻¹, δ_{H} (250 MHz) 1.33 (6H, s, 2 x CH₃), 2.76 (1H, br s, OH), 3.33 (2H, s, 1'-CH₂), 6.36 (2H, s, NH₂), 7.17 (1H, dd, *J* 7.3, 1.0, 6-H), 7.26 (1H, dd, *J* 7.3, 7.3, 5-H) and 7.78 (1H, dd, *J* 7.3, 1.0; 4-H), δ_{C} (101 MHz) 29.74 (2 x CH₃), 43.16 (CH₂), 71.03 (C), 118.15 (CH), 122.80 (C), 123.94 (CH), 130.42 (CH), 131.27 (C) and 143.27 (C), *m/z* [FAB] 207 (100%, M⁺ + H), 191 (5) and 189 (10). [Found; M⁺ + H, 207.1250. C₁₀H₁₅N₄O requires M + H, 207.1246]

7-(2'-Hydroxycyclohexylmethylene)-1H-benzotriazol-1-amine (645)



Following the general procedure, treatment of aminobenzotriazole (640) (50 mg, 0.15 mmol) with TFA yielded the *title compound* (645) (34 mg, 95%) as a colourless gum, ν_{\max} 3244, 2934, 2845, 1452, 964 and 910 cm^{-1} , δ_{H} (250 MHz) 1.50 (10H, br s, 5 x CH_2), 3.24 (2H, s, 1'- CH_2), 7.07-7.20 (2H, m, 5- & 6-H) and 7.73 (1H, dd, J 7.3, 1.0, 4-H), δ_{C} (68 MHz) 22.03 (CH_2), 25.64 (CH_2), 37.70 (CH_2), 42.36 (CH_2), 71.59 (C), 117.75 (CH), 121.42 (C), 123.94 (CH), 130.28 (CH), 130.85 (C) and 144.27 (C), m/z [FAB] 247 (100%, $\text{M}^+ + \text{H}$), 231 (1) and 229 (5). [Found: $\text{M}^+ + \text{H}$, 247.1549. $\text{C}_{13}\text{H}_{19}\text{N}_4\text{O}$ requires $\text{M} + \text{H}$, 247.1559].

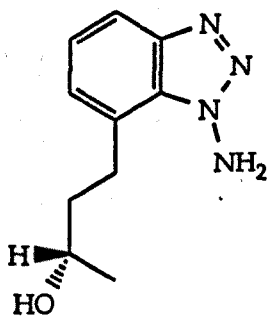
7-(3'-Hydroxypentyl)-1H-benzotriazol-1-amine (659)



Using the general procedure, treatment of aminobenzotriazole (658)

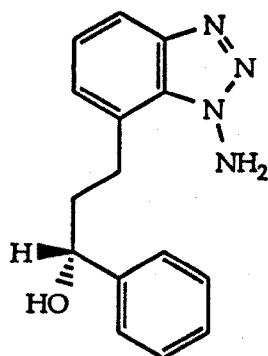
(100 mg, 0.31 mmol) with TFA yielded the *title compound* (659) (52 mg, 75%) as a colourless gum, ν_{\max} 3360, 2930, 1730, 1647, 1470, 1118, 985, 913, 882 and 864 cm^{-1} , δ_{H} (250 MHz) 0.91 (3H, t, J 7.5, 5'-CH₃), 1.43-1.57 (2H, m, 4'-CH₂), 1.73-1.96 (2H, m, 2'-CH₂), 3.35 (2H, t, J 7.5, 1'-CH₂), 3.49-3.62 (1H, m, 3'-CH), 6.30 (2H, s, NH₂), 7.21-7.38 (2H, m, 5- & 6-H) and 7.70-7.80 (1H, m, 4-H), δ_{C} (101 MHz) 9.83 (CH₃), 26.07 (CH₂), 30.05 (CH₂), 38.51 (CH₂), 72.00 (CH), 116.99 (CH), 124.35 (CH), 126.56 (C), 127.84 (CH), 130.29 (C) and 144.71 (C), m/z [FAB] 221 (100%, M⁺ + H) and 207 (25). [Found: M⁺ + H, 221.1403. C₁₁H₁₇N₄O requires M + H, 221.1402].

7-(3'-(S)-(+)-Hydroxybutyl)-1H-benzotriazol-1-amine (683)



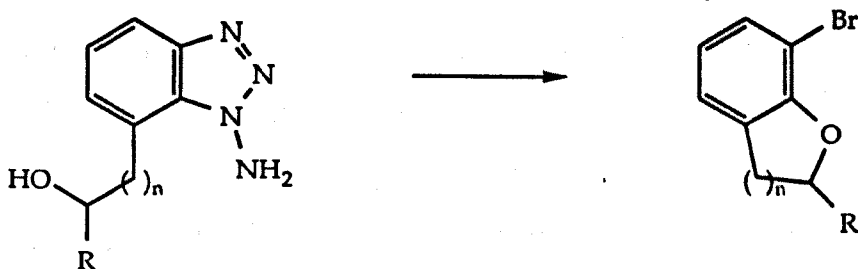
Following the general procedure, treatment of aminobenzotriazole (681) (200 mg, 0.65 mmol) with TFA gave the *title compound* (683) (94 mg, 70%) as a colourless gum, $[\alpha]_{\text{D}} = +9.9$ [(c = 1.9, 25°C, CH₂Cl₂)], ν_{\max} 3367, 2928, 2854, 1635, 1457, 1121, 950 and 903 cm^{-1} , δ_{H} (250 MHz) 1.24 (3H, d, J = 4.2, 4'-CH₃), 1.74-1.89 (2H, m, 2'-CH₂), 3.21 (2H, t, J 7.6, 1'-CH₂), 3.75-3.83 (1H, m, 3'-CH), 5.75 (2H, br s, NH₂), 7.12-7.22 (2H, m, 5- & 6-H) and 7.61-7.75 (1H, m, 4-H), δ_{C} (68 MHz) 23.34 (CH₃), 26.42 (CH₂), 40.77 (CH₂), 66.94 (CH), 117.09 (CH), 124.53 (CH), 126.45 (C), 128.05 (CH), 130.37 (C) and 144.14 (C), m/z [FAB] 207 (100%, M⁺ + H), 191 (8) and 189 (11). [Found: M⁺ + H, 207.1241. C₁₀H₁₅N₄O requires M + H, 207.1246].

7-(3'-(R)-(+)-Hydroxy-3'-phenylpropyl)-1H-benzotriazol-1-amine (684)



Following the general procedure, treatment of aminobenzotriazole (682) (129 mg, 0.35 mmol) with TFA gave the *title compound* (684) (38 mg, 40%) as a colourless gum, $[\alpha]_D = +66.7$ [$c = 0.65$, 25°C , CH_2Cl_2], ν_{max} 3360, 2927, 2854, 1635, 1463, 1124, 1013, 977 and 900 cm^{-1} , δ_{H} (250 MHz) 2.04-2.24 (2H, m, 2'- CH_2), 3.27 (2H, t, J 7.9, 1'- CH_2), 4.64-4.70 (1H, m, 3'-CH), 7.19-7.37 (7H, m, 5-, 6-H and ArH) and 7.71-7.75 (1H, m, 4-H), δ_{C} (68 MHz) 26.54 (CH_2), 40.63 (CH_2), 73.37 (CH), 117.52 (CH), 124.42 (CH), 125.82 (CH), 126.00 (C), 126.41 (CH), 127.55 (CH), 128.01 (CH), 128.12 (CH), 128.39 (C), 131.17 (C) and 144.25 (C), m/z [FAB] 269 (40%, $\text{M}^+ + \text{H}$), 253 (15) and 251 (10). [Found: $\text{M}^+ + \text{H}$, 269.1427. $\text{C}_{15}\text{H}_{17}\text{N}_4\text{O}$ requires $\text{M} + \text{H}$, 269.1402].

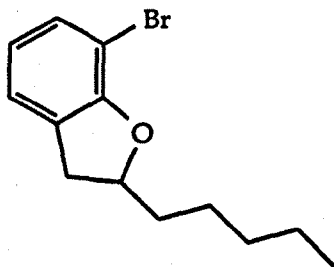
e) Reactions of *ortho*-substituted 1-Aminobenzotriazoles with N-Bromosuccinimide [NBS]



General Procedure:-

To a stirred solution of NBS (2 equivalents) in dichloromethane (0.01 mL mmol⁻¹) at ambient temperature was added dropwise *via* syringe a solution of the aminobenzotriazole (1 equivalent) in dichloromethane (1 mL mmol⁻¹), which resulted in vigorous effervescence, a mild exotherm and the solution turning orange. After leaving to stir at ambient temperature for 1h, the solvent was removed under reduced pressure to furnish a light orange material which was chromatographed using petrol/diethyl ether (9:1) as eluant to give the pure product.

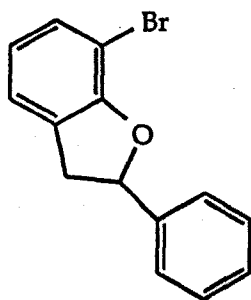
7-Bromo-2-pentyl-2,3-dihydrobenzofuran (647)



Following the general procedure, treatment of the aminobenzotriazole (642) (51 mg, 0.2 mmol) with NBS yielded the *title compound* (647) (25 mg, 45%) as a colourless oil, ν_{\max} 2930, 2856, 1642, 1580, 1459, 1122 and 1009 cm⁻¹, δ_{H} (250 MHz) 0.90 (3H, t, *J* 6.8, 5'-CH₃), 1.29-1.57 (8H, m, 1'-, 2'-, 3'- & 4'-CH₂), 2.81 (1H, dd, *J* 13.6, 8.8, 3-CH_{2A}), 3.11 (1H, dd, *J* 13.7, 8.9, 3-CH_{2B}), 3.83-4.01 (1H, m, 2-CH), 7.12 (1H, dd, *J* 7.7, 7.7, 5-H), 7.22 (1H, dd, *J* 7.7, 1.7, 6-H) and 7.52 (1H, dd, *J* 7.7, 1.7, 4-H), δ_{C} (101 MHz) 14.13 (CH₃), 22.70, 25.39 (CH₂), 31.89 (CH₂), 37.35 (CH₂), 45.37 (CH₂), 71.07 (CH), 126.04 (C), 127.02 (C), 128.16 (CH), 130.44 (CH), 132.09 (CH) and

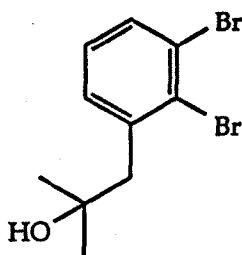
141.40 (C), m/z [EI] 270 (49%, M^+ (^{81}Br)), 268 (53, M^+ (^{79}Br)), 200 (53), 198 (57), 187 (77), 185 (80), 172 (42), 170 (42), 132 (71), 118 (49), 105 (20), 91 (38), 90 (25), 89 (40), 78 (14) and 77 (30). [Found: M^+ , 268.0448. $\text{C}_{13}\text{H}_{17}^{79}\text{BrO}$ requires M , 268.0463].

7-Bromo-2-phenyl-2,3-dihydrobenzofuran (648)



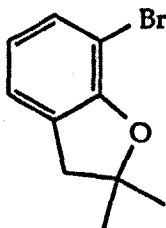
Following the general procedure, treatment of the aminobenzotriazole (641) (25 mg, 0.1 mmol) with NBS gave the *title compound* (648) as a colourless oil (10 mg, 38%), ν_{max} 2980, 2914, 1624, 1480, 1119 and 970 cm^{-1} , δ_{H} (250 MHz) 3.10 (1H, dd, J 13.0, 8.3, 3- CH_2A), 3.45 (1H, dd, J 13.0, 7.5, 3- CH_2B), 4.97 (1H, dd, J 7.6, 7.6, 2'-CH), 7.04 (1H, dd, J 7.6, 7.6, 5-H), 7.21-7.49 (6H, m, 6-H & ArH) and 7.46 (1H, dd, J 7.6, 1.9, 4-H), δ_{C} (101 MHz) 47.96 (CH_2), 73.27 (CH), 125.77 (CH), 126.13 (C), 127.92 (CH), 128.13 (CH), 128.39 (CH), 128.62 (CH), 128.86 (CH), 130.79 (C), 130.97 (CH), 132.30 (CH), 140.71 (C) and 143.81 (C), m/z [EI] 276 (3%, M^+ (^{81}Br)), 274 (5, M^+ (^{79}Br)), 258 (48, $M - \text{H}_2\text{O}$), 256 (47, $M - \text{H}_2\text{O}$), 194 (12), 177 (26), 176 (28), 165 (21), 163 (21), 151 (28), 149 (25), 107 (100), 105 (67), 91 (20) and 77 (37). [Found: M^+ , 273.9992. $\text{C}_{14}\text{H}_{11}^{79}\text{BrO}$ requires M , 273.9993].

1,2-Dibromo-3-(2'-hydroxy-2'-methylpropyl)benzene (649)



Following the general procedure, treatment of the aminobenzotriazole (644) (48 mg, 0.27 mmol) with NBS gave not the desired bromo-dihydrobenzofuran (650), but instead the *title compound* (649) (36 mg, 52%) as a pale yellow oil, ν_{\max} 3592, 2929, 2853, 1580, 1462, 1410, 1110, 970 and 899 cm^{-1} , δ_{H} (250 MHz) 1.29 (6H, s, 2 x CH_3), 3.13 (2H, s, 1'- CH_2), 7.12 (1H, dd, J 7.8, 7.8, 5-H), 7.31 (1H, dd, J 7.8, 1.7, 6-H) and 7.53 (1H, dd, J 7.8, 1.7, 4-H), δ_{C} (101 MHz) 29.57 (CH_3), 29.67 (CH_3), 49.84 (CH_2), 72.14 (C), 108.12 (C), 112.14 (C), 127.14 (C), 127.88 (CH), 130.97 (CH) and 132.20 (CH), m/z [EI] 292 (6%, $\text{M} - \text{H}_2\text{O}$ ($^{81,81}\text{Br}$)), 290 (3, $\text{M} - \text{H}_2\text{O}$ ($^{79,81}\text{Br}$)), 250 (23), 248 (12), 170 (7) and 168 (3). [Found $\text{M} - \text{H}_2\text{O}$, 289.9981. $\text{C}_{10}\text{H}_{10}^{79,81}\text{Br}_2$ requires M , 289.9992].

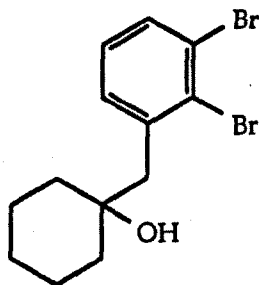
7-Bromo-2,2-dimethyl-2,3-dihydrobenzofuran (650)



In a slight alteration to the general procedure, the

aminobenzotriazole (644) (50 mg, 0.2 mmol) was treated with NBS in the presence of 1-pentene (420 mg, 6 mmol, 30 equivalents) to furnish the *title compound* (650) (25 mg, 45%) as a colourless oil, ν_{\max} 2930, 2855, 1603, 1582, 1462, 1144, 1101, 971, 904, 871 and 648 cm^{-1} , δ_{H} (250 MHz) 1.45 (6H, s, 2 x 2-CH₃), 3.03 (2H, s, 3-CH₂), 6.70 (1H, dd, J 7.7, 7.7, 5-H), 7.06 (1H, dd, J 7.7, 1.3, 6-H) and 7.27 (1H, dd, J 7.7, 1.3, 4-H), δ_{C} (68 MHz) 28.28 (CH₃), 43.78 (CH₂), 87.75 (C), 102.82 (C), 112.65 (C), 121.27 (CH), 124.14 (CH), 128.59 (C) and 131.14 (CH), m/z [EI] 228 (100%, M⁺ (⁸¹Br)), 226 (98, M⁺ (⁷⁹Br)), 210 (17), 186 (20), 147 (18), 145 (67), 120 (15) and 104 (20). [Found: M⁺, 225.9811. C₁₀H₁₁⁷⁹BrO requires M, 225.9993].

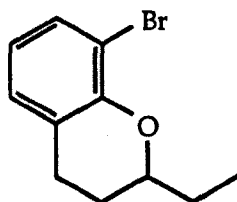
1,2-Dibromo-3-(2'-hydroxycyclohexylmethylene)benzene (651)



Following the modified procedure used for the aminobenzotriazole (644), treatment of the aminobenzotriazole (645) (35 mg, 0.14 mmol) with NBS in the presence of 1-pentene (294 mg, 4.2 mmol, 30 equivalents) yielded not the desired bromo-dihydrobenzofuran but the *title compound* (651) (25 mg, 51%) as a pale yellow oil, ν_{\max} 3591, 2933, 2854, 1579, 1450, 1410, 1127, 1096, 979, 956, 905 and 860 cm^{-1} , δ_{H} (250 MHz) 1.11-1.61 (10H, s, 5 x CH₂), 3.07 (2H, s, 1'-CH₂), 7.08 (1H, dd, J 7.7, 7.7, 5-H), 7.27 (1H, dd, J 7.7, 1.6, 6-H) and 7.49 (1H, dd, J 7.7, 1.6, 4-H), δ_{C} (101 MHz) 21.84 (2 x CH₂), 25.64 (CH₂), 37.40 (2 x CH₂), 49.58 (CH₂), 72.49 (C), 126.64 (C),

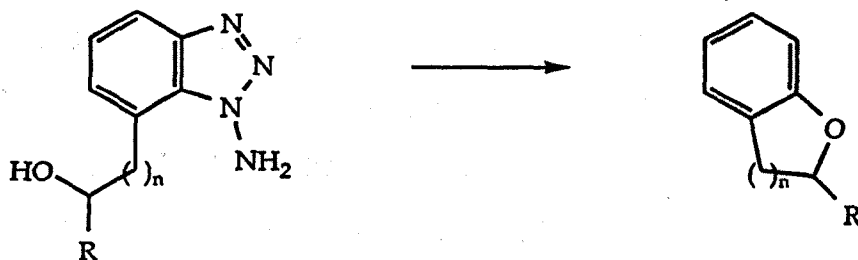
127.64 (CH), 127.97 (C), 131.03 (CH), 131.99 (CH) and 139.28 (C), m/z [FAB] 331 (30%, $M - H_2O$, $^{79,81}Br$), 267 (20), 250 (30), 249 (42) and 248 (25). [Found: $M - H_2O$, 331.0719. $C_{13}H_{15}^{79,81}Br_2$ requires M , 331.0725].

8-Bromo-3,4-dihydro-2-ethyl-2H-1-benzopyran (660)



Following the general procedure above, treatment of the aminobenzotriazole (659) (45 mg, 0.2 mmol) with NBS yielded the *title compound* (660) (26 mg, 53%) as a colourless oil, ν_{max} 3402, 2929, 1694, 1602, 1458, 1409, 1097, 981 and 908 cm^{-1} , δ_H (250 MHz) 0.97 (3H, t, J 7.5, 2'-CH₃), 1.46-1.83 (4H, m, 3-CH₂ & 1'-CH₂), 2.84-3.02 (2H, m, 4-CH₂), 3.55-3.64 (1H, m, 2-CH), 7.09 (1H, dd, J 7.7, 7.7, 6-H), 7.20 (1H, dd, J 7.7, 1.7, 7-H) and 7.48 (1H, dd, J 7.7, 1.7, 5-H), δ_C (101 MHz) 9.95 (CH₃), 30.40 (CH₂), 34.40 (CH₂), 38.85 (CH₂), 72.25 (CH), 126.08 (C), 126.65 (C), 128.35 (CH), 129.03, 131.57 (CH) and 144.61 (C), m/z [EI] 242 (11%, M^+ (^{81}Br)), 240 (17, M^+ (^{79}Br)), 211 (72), 209 (67), 185 (24), 183 (25), 171 (15), 169 (15), 167 (25), 102 (15) and 77 (15). [Found: M^+ , 240.0142. $C_{11}H_{13}^{79}BrO$ requires M , 240.0149].

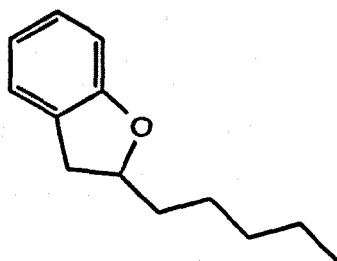
f) Reactions of *ortho*-substituted 1-Aminobenzotriazoles with Lead(IV) Acetate



General Procedure:-

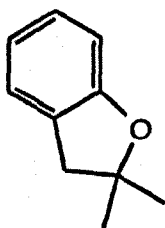
To a stirred suspension of lead(IV) acetate (1.1 equivalents) in dichloromethane (0.1 mmol mL^{-1}) at ambient temperature was added dropwise *via* syringe a solution of the aminobenzotriazole (1 equivalent) in dichloromethane (1 mL mmol^{-1}), which resulted in vigorous effervescence and a mild exotherm being observed. After stirring at ambient temperature for 1h, the mixture was filtered through Celite, with the filter cake washed with diethyl ether ($2 \times 30 \text{ mL}$) and the combined organic filtrates evaporated to yield a crude material which was chromatographed using petrol/diethyl ether (9:1) as eluant to give the purified product.

2-Pentyl-2,3-dihydrobenzofuran (656)



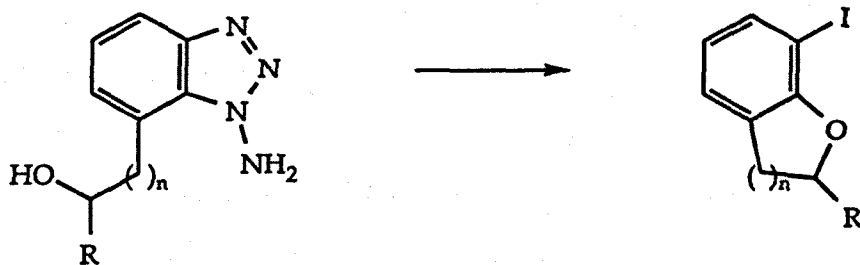
Following the general procedure, treatment of the aminobenzotriazole (642) (19 mg, 0.08 mmol) with lead (IV) acetate yielded the *title compound* (656) (9.5 mg, 65%) as a colourless oil, ν_{\max} 2928, 2854, 1650, 1463, 1100 and 1009 cm^{-1} , δ_{H} (250 MHz) 0.91 (3H, t, J 6.8, 5'-CH₃), 1.33-1.71 (7H, m, 1'-CH_{2A}, 2'-, 3'- & 4'-CH₂), 1.77-1.86 (1H, m, 1'-CH_{2B}), 2.84 (1H, dd, J 15.5, 7.9, 3-CH_{2A}), 3.26 (1H, dd, J 15.4, 8.9, 3-CH_{2B}), 4.74-4.79 (1H, m, 2-CH), 6.75 (1H, dd, J 7.6, 1.0, 4-H), 6.81 (H, dd, J 7.6, 7.6, 5-H), 7.10 (1H, dd, J 7.6, 7.6, 6-H) and 7.14 (1H, dd, J 7.6, 1.0, 7-H), δ_{C} (101 MHz) 14.10 (CH₃), 22.68 (CH₂), 25.22 (CH₂), 31.63 (CH₂), 35.58 (CH₂), 36.17 (CH₂), 83.49 (CH), 109.33 (CH), 120.12 (CH), 124.98 (CH), 127.96 (CH), 127.07 (C) and 159.71 (C), m/z [EI] 190 (31%, M⁺), 133 (54), 120 (44), 119 (51), 108 (14), 107 (100), 91 (22), and 77 (10). [Found: M⁺, 190.1344. C₁₃H₁₈O requires M, 190.1358].

2,2-Dimethyl-2,3-dihydrobenzofuran (657)



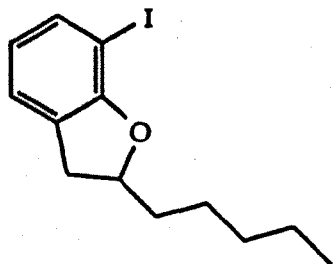
Following the general procedure, treatment of the aminobenzotriazole (644) (21 mg, 0.12 mmol) with lead(IV) acetate yielded the *title compound*²³⁷ (657) (11 mg, 75%) as a colourless oil, ν_{\max} 2928, 2854, 1590, 1459, 1100 and 1009 cm^{-1} , δ_{H} (250 MHz) 1.48 (6H, s, 2 x 2-CH₃), 3.01 (2H, s, 3-CH₂), 6.98 (1H, dd, J 7.6, 1.0, 4-H), 7.07 (1H, dd, J 7.6, 7.6, 5-H), and 7.33-7.40 (2H, m, 6- & 7-H), m/z [EI] 148 (4%, M⁺), 133 (10), 120 (60), 107 (25) and 95 (22). [Found M⁺, 148.0863. Calc. for C₁₀H₁₂O: M, 148.0888].

g) Reactions of *ortho*-substituted 1-Aminobenzotriazoles with N-Iodosuccinimide [NIS]



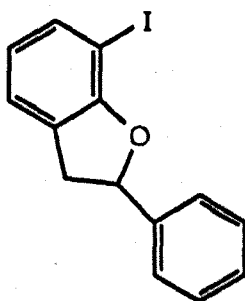
To a stirred solution of NIS (2.5 equivalents) in dichloromethane (0.1 mmol mL⁻¹) at ambient temperature in the dark was added dropwise *via* syringe a solution of the aminobenzotriazole (1 equivalent) in dichloromethane (1 mmol mL⁻¹), which resulted in vigorous effervescence, a mild exotherm and the solution turning purple. After stirring at ambient temperature for a further 1h, the mixture was washed with saturated aqueous sodium thiosulphate (10 mL), water (10 mL) and brine (10 mL), and the separated organic layer dried and evaporated to yield a dark brown material which was chromatographed using petrol/diethyl ether (9:1) as eluant to yield the pure product.

7-Iodo-2-pentyl-2,3-dihydrobenzofuran (676)



Following the general procedure above, treatment of the aminobenzotriazole (642) (30 mg, 0.12 mmol) with NIS yielded the *title compound* (676) (35 mg, 92%) as a colourless oil, ν_{\max} 2981, 2858, 1599, 1579, 1457, 1117, 984, 897 and 869 cm^{-1} , δ_{H} (250 MHz) 0.94 (3H, t, J 6.6, 5'-CH₃), 1.10-1.70 (7H, m, 1'-CH_{2A}, 2'-, 3'- & 4'-CH₂), 1.81-1.90 (1H, m, 1'-CH_{2B}), 2.97 (1H, dd, J 15.5, 7.6, 3-CH_{2A}), 3.40 (1H, dd, J 15.5, 8.8, 3-CH_{2B}), 4.75-4.90 (1H, m, 2-CH), 6.58 (1H, dd, J 7.8, 7.8, 5-H), 7.10 (1H, d, J 7.8, 6-H) and 7.45 (1H, d, J 7.8, 4-H), δ_{C} (101 MHz) 14.00 (CH₃), 22.52 (CH₂), 24.55 (CH₂), 29.69 (CH₂), 31.65 (CH₂), 36.59 (CH₂), 83.10 (C-I), 83.27 (CH), 121.89 (CH), 124.76 (CH), 127.82 (C), 136.62 (CH) and 142.87 (C), m/z [EI] 317 (15%, M⁺ (¹²⁸I)), 316 (88, M⁺ (¹²⁷I)), 246 (50), 234 (14), 233 (100), 118 (44) and 105 (28), 91 (10), 90 (13), 89 (14), 78 (14) and 77 (18). [Found: M⁺, 316.0302. C₁₃H₁₇¹²⁷IO requires M, 316.0324].

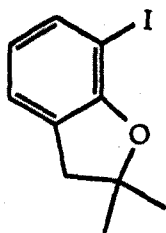
7-Iodo-2-phenyl-2,3-dihydrobenzofuran (677)



Following the general procedure above, treatment of the aminobenzotriazole (641) (37 mg, 0.15 mmol) with NIS gave the *ititle compound* (677) (39 mg, 81%) as a colourless oil, ν_{\max} 2928, 2854, 1600, 1580, 1491, 1120, 973, 909 and 871 cm^{-1} , δ_{H} (250 MHz) 3.31 (1H, dd, J 15.8, 9.5, 3-CH_{2A}), 3.40 (1H, dd, J 15.8, 8.0, 3-CH_{2B}), 5.85 (1H, dd, J 7.7, 7.7, 2-CH), 6.65 (1H, dd, J 7.7, 7.7, 5-H), 7.12 (1H, dd, J 7.7, 1.1, 6-H), 7.32-7.40 (5H, m,

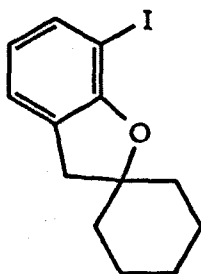
ArH) and 7.52 (1H, dd, J 7.7, 1.1, 4-H), δ_C (68 MHz) 39.77 (CH₂), 82.41 (C-I), 83.21 (CH), 122.53 (CH), 124.74 (CH), 125.54 (CH), 125.62 (CH), 125.82 (C), 128.09 (CH), 128.66 (CH), 136.96 (CH), 136.62 (CH), 142.87 (C) and 145.71 (C), m/z [EI] 323 (20%, M⁺ (¹²⁸I)), 322 (100, M⁺ (¹²⁷I)), 244 (5), 194 (20), 165 (27), 152 (11), 118 (5), 105 (3), 89 (10) and 77 (5). [Found: M⁺, 321.9904. C₁₄H₁₁¹²⁷IO requires M, 321.9855].

2,2-Dimethyl-7-iodo-2,3-dihydrobenzofuran (678)



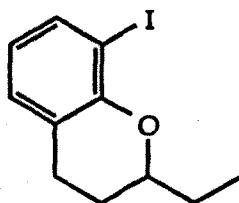
Following the general procedure above, treatment of the aminobenzotriazole (644) (100 mg, 0.49 mmol) with NIS gave the *title compound* (678) (126 mg, 95%) as a colourless oil, ν_{\max} 2929, 2854, 1599, 1577, 1459, 1142, 1099, 970, 890 and 871 cm⁻¹, λ_{\max} 209, 294 and 309 nm, δ_H (250 MHz) 1.44 (6H, s, 2 x 2-CH₃), 3.04 (2H, s, 3-CH₂), 6.49 (1H, dd, J 7.5, 7.5, 5-H), 7.00 (1H, dd, J 7.5, 1.0, 6-H) and 7.38 (1H, dd, J 7.5, 1.0, 4-H), δ_C (68 MHz) 28.16 (2 x CH₃), 44.12 (CH₂), 74.12 (C), 88.12 (C-I), 121.67 (CH), 124.94 (CH), 125.74 (C), 136.73 (CH) and 144.12 (C), m/z [EI] 274 (100%, M⁺ (¹²⁷I)), 259 (16), 147 (10), 146 (5), 132 (72), 131 (32), 119 (23), 103 (8), 91 (15), 89 (17) and 77 (17). [Found: M⁺, 273.9830. C₁₀H₁₁¹²⁷IO requires M, 273.9855].

Spiro-2-(2,3-dihydrobenzofuran-7-iodo)cyclohexane (679)



Following the general procedure above, treatment of the aminobenzotriazole (645) (35 mg, 0.14 mmol) with NIS furnished the *title compound* (679) (37 mg, 82%) as a colourless oil, ν_{\max} 2940, 2856, 1598, 1577, 1457, 1126, 1110, 946, 916 and 860 cm^{-1} , δ_{H} (250 MHz) 1.27-1.91 (10H, m, 5 x CH_2), 3.08 (2H, s, 3- CH_2), 6.59 (1H, dd, J 7.7, 7.7, 5-H), 7.07 (1H, dd, J 7.7, 1.1, 6-H) and 7.44 (1H, dd, J 7.7, 1.1, 4-H), δ_{C} (68 MHz) 22.88, 22.97 (CH_2), 25.11 (CH_2), 36.88 (CH_2), 36.97 (CH_2), 42.18 (CH_2), 76.53 (C), 88.31 (C-I), 121.49 (CH), 124.98 (CH), 126.78 (C), 136.57 (CH) and 138.21 (C), m/z 315 (16%, M^+ (^{128}I)), 314 (75, M^+ (^{127}I)), 246 (10), 234 (16), 233 (66), 186 (5), 105 (18), 81 (100), 80 (34) and 77 (18). [Found: M^+ , 314.0161. $\text{C}_{13}\text{H}_{15}^{127}\text{IO}$ requires M , 314.0168].

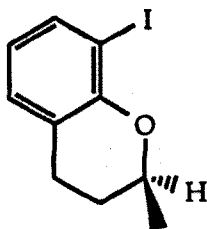
3,4-Dihydro-2-ethyl-8-iodo-2H-1-benzopyran (680)



Following the general procedure, treatment of the

aminobenzotriazole (659) (83 mg, 0.38 mmol) with NIS yielded the *title compound* (680) (65 mg, 63%) as a colourless oil, ν_{\max} 2939, 2848, 1714, 1594, 1562, 1459, 1119, 979, 944, 904, 863 and 837 cm^{-1} , δ_{H} (250 MHz) 1.14 (3H, t, J 7.4, 2'-CH₃), 1.58-1.88 (3H, m, 3-CH_{2A} and 1'-CH₂), 1.96-2.06 (1H, m, 3-CH_{2B}), 2.68-2.93 (2H, m, 4-CH₂), 3.96-4.06 (1H, m, 2-CH), 6.58 (1H, t, J 7.7, 7.7, 6-H), 7.02 (1H, dd, J 7.7, 0.6, 7-H) and 7.57 (1H, dd, J 7.7, 0.6, 5-H), δ_{C} (68 MHz) 9.94 (CH₃), 25.02 (CH₂), 27.14 (CH₂), 28.28 (CH₂), 78.51 (CH), 85.74 (C-I), 121.44 (CH), 123.05 (C), 129.59, 136.85 (CH) and 153.12 (C), m/z [EI] 288 (69%, M⁺ (¹²⁷I)), 259 (7), 246 (6), 234 (8), 233 (100), 132 (28), 118 (6), 105 (19), 78 (10) and 77 (14). [Found: M⁺, 288.0011. C₁₁H₁₃¹²⁷IO requires M, 288.0011].

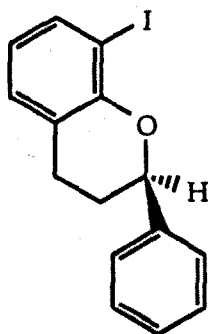
3,4-Dihydro-2-(S)-(-)-methyl-8-iodo-2H-1-benzopyran (685)



Following the general procedure above, treatment of the aminobenzotriazole (683) (31 mg, 0.15 mmol) with NIS gave the *title compound* (685) (28 mg, 68%) as a colourless oil, $[\alpha]_{\text{D}} = -44.1$ [$c = 0.32$, 25°C, CH₂Cl₂], ν_{\max} 2935, 2848, 1595, 1562, 1461, 1121, 1103, 1076, 949, 940, 906 and 848 cm^{-1} , δ_{H} (250 MHz) 1.46 (3H, d, J 6.3, 1'-CH₃), 1.60-1.80 (1H, m, 3-CH_{2A}), 1.95-2.10 (1H, m, 3-CH_{2B}), 2.66-2.90 (2H, m, 4-CH₂), 4.14-4.34 (1H, m, 2-CH), 6.58 (1H, dd, J 7.6, 7.6, 5-H), 7.02 (1H, dd, J 7.6, 1.0, 6-H) and 7.58 (1H, dd, J 7.6, 1.0, 4-H), δ_{C} (68 MHz) 21.10 (CH₃), 25.02 (CH₂), 29.06 (CH₂), 73.48 (CH), 88.31 (C-I), 121.49 (CH), 122.12 (C), 129.65 (CH), 136.97 (CH) and

143.42 (C), m/z [EI] 275 (11%, M^+ (^{128}I)), 274 (100, M^+ (^{127}I)), 233 (56), 232 (16), 147 (7), 132 (27), 131 (40), 118 (10), 105 (19), 91 (5), 89 (4), 78 (7) and 77 (13). [Found: M^+ , 273.9855. $\text{C}_{10}\text{H}_{11}^{127}\text{IO}$ requires M , 273.9861].

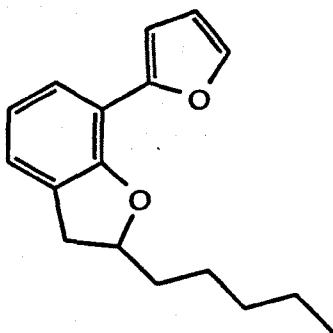
3,4-Dihydro-8-iodo-2-(R)-(+)-phenyl-2H-1-benzopyran (684)



Following the general procedure, treatment of the aminobenzotriazole (684) (33 mg, 0.12 mmol) with NIS furnished the *title compound* (686) (32mg, 77%) as a colourless oil, $[\alpha]_D = +25.6$ [(c = 0.36, 25°C, CH_2Cl_2)], ν_{max} 2926, 2854, 1684, 1595, 1564, 1494, 1450, 1128, 1092, 997 and 904 cm^{-1} , δ_{H} (250 MHz) 1.95-2.20 (1H, m, 3- CH_2A), 2.20-2.40 (1H, m, 3- CH_2B), 2.70-2.85 (1H, m, 4- CH_2A), 2.90-3.05 (1H, m, 4- CH_2B), 5.24 (1H, dd, J 9.5, 2.5, 2-CH), 6.64 (1H, dd, J 7.6, 7.6, 6-H), 7.05 (1H, d, J 7.6, 7-H), 7.24-7.58 (5H, m, ArH) and 7.64 (1H, d, J 7.6, 5-H), δ_{C} (68 MHz) 25.61 (CH_2), 29.12 (CH_2), 77.84 (CH), 88.15 (C-I), 122.74 (C), 125.54 (2 x CH), 126.54 (CH), 128.46 (2 x CH), 129.29 (CH), 136.44 (CH), 142.71 (C) and 143.71 (C), m/z [EI] 337 (20%, M^+ (^{128}I)), 336 (100, M^+ (^{127}I)), 245 (10), 244 (10), 232 (20), 209 (29), 155 (11), 118 (31), 105 (84), 104 (49), 91 (38) and 77 (48). [Found: M^+ , 336.0016. $\text{C}_{15}\text{H}_{13}^{127}\text{IO}$ requires M , 336.0011].

h) Coupling Reactions of Iodo-Dihydrobenzofurans and Iodo-Chromans

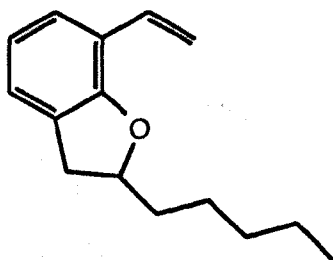
7-Furanyl-2-pentyl-2,3-dihydrobenzofuran (688)



To a solution of the iodo-dihydrobenzofuran (676) (23 mg, 7.2×10^{-5} mol, 1 equivalent) in dry tetrahydrofuran (3 mL) was added dichloro-bis-triphenylphosphine palladium(0) (3 mg) and tri-*n*-butyl(2-furyl)stannane²⁵⁶ (28 mg, 7.91×10^{-5} mol, 1.1 equivalents). The mixture was refluxed for 16h, then cooled and the solvent removed under reduced pressure to yield a residue which was taken up in diethyl ether (30 mL) and filtered through alumina. The filter cake was washed with diethyl ether (2 x 50 mL), and the combined filtrates evaporated to yield a residue which was separated by chromatography using petrol/ethyl acetate (99:1) as the eluant to give the *title compound* (688) (30%) as a colourless oil, ν_{\max} 2931, 2858, 1598, 1464, 1156, 1014, 987, 908, 886 and 870 cm^{-1} , λ_{\max} 224, 269, 280, 307 and 320 nm, δ_{H} (250 MHz) 0.95 (3H, t, J 6.9, 5'-CH₃), 1.36-1.78 (7H, 1'-CH_{2A}, 2'-, 3'- & 4'-CH₂), 1.82-1.96 (1H, m, 1'-CH_{2B}), 2.88 (1H, dd, J 15.6, 7.8, 3-CH_{2A}), 3.32 (1H, dd, J 15.3, 8.9, 3-CH_{2B}), 4.84-4.96 (1H, m, 2-CH), 6.50 (1H, dd, J 3.2, 1.8, 4''-H), 6.88 (1H, dd, J 7.5, 7.5, 5-H), 6.90 (1H, d, J 3.2, 3''-H), 7.06 (1H, dd, J 7.5, 0.5, 4-H), 7.45 (1H, d, J 1.8, 5''-H) and 7.58 (1H, dd,

J 7.5, 0.5, 6-H), δ_C (68 MHz) 14.95 (CH₃), 23.51 (CH₂), 26.29 (CH₂), 32.14 (CH₂), 36.35 (CH₂), 37.16 (CH₂), 84.87 (CH), 109.47 (CH), 112.59 (CH), 115.21 (C), 121.17 (CH), 123.90 (CH), 124.30 (CH), 128.48 (C), 142.01 (CH), 152.15 (C) and 156.14 (C), m/z [EI] 256 (100%, M⁺), 199 (32), 186 (15), 173 (87), 172 (30), 157 (11), 144 (13), 128 (10), 115 (15), 91 (10) and 77 (5). [Found: M⁺, 256.1455. C₁₇H₂₀O₂ required M, 256.1463].

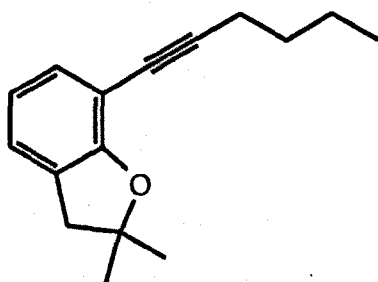
7-Ethenyl-2-pentyl-2,3-dihydrobenzofuran (690)



To a solution of the iodo-dihydrobenzofuran (676) (29 mg, 0.11 mmol, 1 equivalent) in dry tetrahydrofuran (3 mL) was added dichloro-bis-triphenylphosphine palladium(0) (3 mg), and vinyltri-*n*-butyltin (40 mg, 0.127 mmol, 1 equivalent). The mixture was refluxed for 16h, then cooled and the solvent removed under reduced pressure, with the residue taken up in diethyl ether (30 mL) and filtered through alumina. The filter cake was washed with further portions of diethyl ether (2 x 50 mL) and the combined filtrates evaporated to yield a residue which was separated by chromatography using petrol as the eluant to give the *title compound* (690) (20 mg, 87%) as a colourless oil, ν_{\max} 2932, 2858, 1624, 1453, 995, 912 and 863 cm⁻¹, λ_{\max} 220, 252, 312 and 345 nm, δ_H (250 MHz) 0.91-0.95 (3H, t, J 6.9, 5'-CH₃), 1.34-1.92 (8H, m, 1'-, 2'-, 3'- & 4'-CH₂), 2.83 (1H, dd, J 15.4, 8.8, 3-CH_{2A}), 3.25 (1H, dd, J 15.5, 8.8, 3-CH_{2B}), 4.76-4.88 (1H, m, 2-CH), 5.28 (1H, dd, J 11.3, 1.6, 2''-CH_{2A}), 5.92 (1H, dd, J 17.6, 1.6, 2''-CH_{2B}), 6.74 (1H,

dd, J 17.6, 11.3, 1''-CH), 6.78 (1H, dd, J 7.5, 7.5, 5-H), 7.04 (1H, dd, J 7.5, 0.5, 5-H) and 7.13 (1H, dd, J 7.5, 0.5, 4-H), δ_C (101 MHz) 14.02 (CH₃), 22.58 (CH₂), 25.21 (CH₂), 31.69 (CH₂), 35.31 (CH₂), 36.16 (CH₂), 76.53 (C), 83.60 (CH), 115.33 (CH₂), 120.04 (CH), 120.21 (C), 123.92 (CH), 126.07 (CH), 127.51 (C), 132.18 (CH) and 157.34 (C), m/z [EI] 216 (77%, M⁺), 159 (41), 145 (24), 133 (100), 131 (60), 117 (22), 115 (23), 91 (9) and 77 (7). [Found: M⁺, 216.1503. C₁₅H₂₀O requires M, 216.1514].

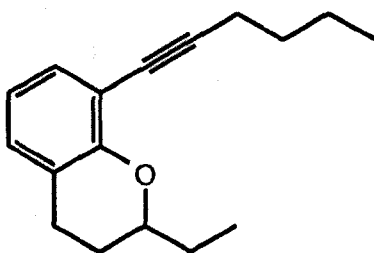
1-(2',2'-Dimethyl-2',3'-dihydrobenzofuran-7'-yl)hexyne (693)



To a solution of the iodo-dihydrobenzofuran (678) (45 mg, 0.14 mmol, 1 equivalent) in dry diethylamine (3 mL) was added copper(I) iodide (7 mg, 4 mol %), dichloro-*bis*-triphenylphosphine palladium(0) (15 mg, 1 mol %) and 1-hexyne (14 mg, 0.17 mmol, 1.2 equivalents). After refluxing for 16h, the mixture was cooled and evaporated to give a residue which was separated by chromatography using petrol as eluant to yield the *title compound* (693) (26 mg, 80%) as a yellow oil, ν_{\max} 2932, 2858, 2216, 1592, 1443, 1167, 1137, 969 and 881 cm⁻¹, λ_{\max} 217, 243, 254 and 309 nm, δ_H (250 MHz) 0.91 (3H, t, J 7.1, 6-CH₃), 1.46-1.66 (4H, m, 4- & 5-CH₂), 1.50 (6H, s, 2 x 2'-CH₃), 2.45 (2H, t, J 7.0, 3-CH₂), 2.99 (2H, s, 3'-CH₂), 6.72 (1H, dd, J 7.6, 7.6, 5'-H), 7.30 (1H, dd, J 7.6, 1.0, 6'-H) and 7.14 (1H, dd, J 7.6, 1.0, 4'-H), δ_C (68 MHz) 13.66 (CH₃), 19.54 (CH₂), 22.00 (CH₂), 28.21 (2 x CH₃), 30.89

(CH₂), 42.91 (CH₂), 76.07 (C), 87.10 (C), 93.77 (C), 106.00 (C), 119.64 (CH), 124.46 (CH), 127.10 (C), 131.59 (CH) and 158.14 (C), *m/z* [EI] 228 (100%, M⁺), 213 (28), 186 (18), 185 (64), 171 (24), 157 (13), 145 (19), 128 (11) and 115 (17). [Found: M⁺, 228.1527. C₁₆H₂₀O requires M, 228.1514].

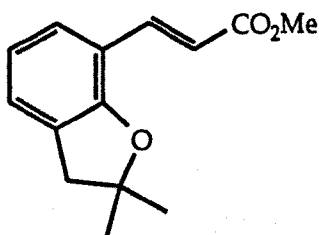
1-(2'-Ethyl-3',4'-dihydro-2H-1-benzopyran-8'-yl)hexyne (694)



To a solution of the iodo-chroman (680) (26 mg, 0.09 mmol, 1 equivalent) in dry diethylamine (2 mL) was added copper(I) iodide (0.8 mg, 4 mol %), dichloro-*bis*-triphenylphosphine palladium(0) (0.25 mg, 1 mol %) and 1-hexyne (10 mg, 0.12 mmol, 1.2 equivalents). The mixture was refluxed for 16h, then cooled and the solvent removed under reduced pressure to yield a residue which was subjected to column chromatography using petrol as eluant to yield the *title compound* (694) (16 mg, 75%) as a yellow oil, ν_{\max} 2900, 2860, 2226, 1590, 1464, 1140, 908 and 880 cm⁻¹, λ_{\max} 216, 249, 257, and 305 nm, δ_{H} (250 MHz) 0.95 (3H, t, *J* 7.5, 6-CH₃), 1.10 (3H, t, *J* 7.1, 2''-CH₃), 1.45-2.06 (8H, m, 4-, 5-, 3'- & 1''-CH₂), 2.48 (2H, t, *J* 6.7, 3-CH₂), 2.67-2.90 (2H, m, 4'-CH₂), 3.92-4.03 (1H, m, 2'-CH), 6.72 (1H, dd, *J* 7.5, 7.5, 5'-H), 6.96 (1H, dd, *J* 7.5, 1.0, 6'-H) and 7.28 (1H, dd, *J* 7.5, 1.0, 4'-H), δ_{C} (68 MHz) 9.76 (CH₃), 13.66 (CH₃), 19.54 (CH₂), 21.93 (CH₂), 24.82 (CH₂), 26.83 (CH₂), 28.29 (CH₂), 30.93 (CH₂), 76.57 (C), 77.66 (CH), 93.15 (C), 112.42 (C), 119.25 (CH), 121.45 (C), 128.92 (CH), 131.59 (CH) and 153.34

(C), m/z [EI] 242 (100%, M^+), 213 (16), 212 (16), 199 (18), 188 (21), 187 (93), 171 (18), 157 (20), 145 (38), 144 (23), 115 (29) and 113 (25). [Found: M^+ , 242.1659. $C_{17}H_{22}O$ requires M , 242.1671].

Methyl 3-(2',2'-dimethyl-2',3'-dihydrobenzofuran-7'-yl)propenoate (696)



To a solution of palladium(II) acetate (0.25 mg, 2 mol %) and triphenylphosphine (1.2 mg, 8 mol %) in dry dimethylformamide [DMF] (5 mL) under argon at ambient temperature was added the iodo-dihydrobenzofuran (678) (15 mg, 5.5×10^{-5} mol, 1 equivalent), anhydrous sodium acetate (5 mg, 1.1 equivalents) and methyl acrylate (6 mg, 6.0×10^{-4} mol, 1.1 equivalents). After refluxing for 22h, the reaction was allowed to cool to ambient temperature, deionized water (5 mL) was added, and the resulting mixture was washed with petrol (3 x 10 mL). The combined organic extracts were dried and evaporated to yield a residue which was separated by chromatography using petrol/ethyl acetate (99:1) as eluant to give the *title compound* (696) (8 mg, 62%) as a pale yellow oil, ν_{\max} 2951, 1704, 1630, 1606, 1450, 1174, 1137, 988 and 879 cm^{-1} , λ_{\max} 223, 280 and 338 nm, δ_H (250 MHz) 1.52 (6H, s, 2 x 2'-CH₃), 3.02 (2H, s, 3'-CH₂), 3.81 (3H, s, CO₂CH₃), 6.71 (1H, d, J 16.2, 3-CH), 6.83 (1H, dd, J 7.6, 7.6, 5'-H), 7.14 (1H, dd, J 7.6, 1.0, 6'-H), 7.19 (1H, dd, J 7.6, 1.0, 4'-H) and 7.70 (1H, d, J 16.2, 2-CH), δ_C (68 MHz) 28.48 (2 x CH₃), 42.47 (CH₂), 51.62 (CH₃), 88.04 (C), 117.25 (C), 118.90 (CH), 120.20 (CH), 126.79 (CH), 128.16 (C), 128.94 (CH), 130.42 (C),

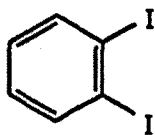
141.15 (CH) and 158.91 (C=O), m/z [EI] 232 (100%, M^+), 201 (7), 200 (23), 199 (13), 185 (9), 159 (4), 157 (4), 113 (10) and 85 (12). [Found: M^+ , 232.1085. $C_{14}H_{16}O_3$ requires M , 232.1099].

i) Reactions of 1-Aminobenzotriazole with N-Iodosuccinimide [NIS]

General Procedure:-

To a stirred solution of NIS (2.5 equivalents) in the chosen solvent (0.1 mmol mL⁻¹) at ambient temperature in the dark was added dropwise *via* syringe a solution of 1-aminobenzotriazole (204) (1 equivalent) in the same solvent (1 mmol mL⁻¹), which resulted in vigorous effervescence, a mild exotherm and the solution turning purple. After stirring at ambient temperature for a further 1h, the mixture was washed with saturated aqueous sodium thiosulphate (10 mL), water (10 mL) and brine (10 mL). The separated organic layer was dried and evaporated to yield a dark brown material which was chromatographed using petrol/ethyl acetate (9:1) as the eluant to yield the pure product.

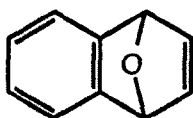
1,2-Diiodobenzene (196)



Using dichloromethane as the solvent in the general procedure, treatment of 1-aminobenzotriazole (204) (150 mg, 1.2 mmol) with NIS (630 mg, 2.8 mmol) gave the title compound (196) (60 mg, 54%) as a light

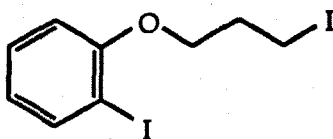
orange oil, δ_{H} (250 MHz) 6.95-7.05 (2H, m, 3- & 6-H) and 7.70-7.88 (2H, m, 4- & 5-H).

1,4-Dihydro-1,4-epoxynaphthalene (105)



Using dry, distilled furan as the solvent in the general procedure, treatment of 1-aminobenzotriazole (204) (100 mg, 0.68 mmol) with NIS (380 mg, 1.69 mmol) gave the title compound (105) (48 mg, 49%) as off-white crystals, m.p. 52-53°C (lit.⁴² 53-55°C).

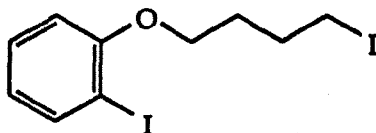
1-Iodo-3-(2'-iodophenoxy)propane (706)



Using oxetane as the solvent in the general procedure, treatment of 1-aminobenzotriazole (204) (50 mg, 0.4 mmol) with NIS (210 mg, 1 mmol) gave the title compound (706) (34 mg, 30%) as an orange-brown gum, ν_{max} 3002, 2930, 2877, 1582, 1478, 1464, 1440, 1179, 1162, 1120, 1054, 1018, 914 and 651 cm^{-1} , δ_{H} (250 MHz) 2.33 (2H, quin, J 6.2, 2- CH_2), 3.42 (2H, t, J 6.6, 1- CH_2), 4.10 (2H, t, J 5.9, 3- CH_2), 6.74 (1H, dd, J 7.6, 7.6, 5'-H), 6.85 (1H, dd, J 7.6, 1.1, 6'-H), 7.31 (1H, dd, J 7.6, 7.6, 4'-H) and 7.78 (1H, dd, J 7.6, 1.1, 3'-H), δ_{C} (68 MHz) 4.41 (CH_2), 32.80 (CH_2), 68.29 (CH_2), 84.15 (C-I), 112.18 (CH), 122.76 (CH), 129.47 (CH), 139.39 (CH) and 153.12 (C), m/z [EI] 388

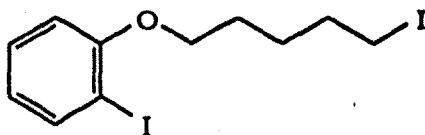
(100%, M^+ (^{127}I)), 220 (65), 203 (16), 169 (95), 134 (17), 106 (20), 92 (21) and 76 (20). [Found: M^+ , 387.8777. $\text{C}_9\text{H}_{10}^{127}\text{I}_2\text{O}$ requires M , 387.8821].

1-Iodo-4-(2'-iodophenoxy)butane (701)



Using tetrahydrofuran as the solvent in the general procedure, treatment of 1-aminobenzotriazole (204) (100 mg, 0.7 mmol) with NIS (420 mg, 2 mmol) gave the *title compound* (701) (38 mg, 14%) as an orange-brown oil, ν_{max} 3001, 2945, 2875, 1582, 1455, 1440, 1162, 1121, 1051, 1018, 942, 908 and 650 cm^{-1} , δ_{H} (250 MHz) 1.89-2.20 (4H, m, 2- & 3- CH_2), 3.30 (2H, t, J 6.3, 1- CH_2), 4.02 (2H, t, J 6.3, 4- CH_2), 6.68 (1H, dd, J 7.7, 7.7, 5'-H), 6.80 (1H, dd, J 7.7, 1.0, 6'-H), 7.29 (1H, dd, J 7.7, 7.7, 4'-H) and 7.78 (1H, dd, J 7.7, 1.0, 3'-H), δ_{C} (68 MHz) 8.00 (CH_2), 30.32 (CH_2), 30.64 (CH_2), 68.25 (CH_2), 88.15 (C-I), 112.45 (CH), 122.76 (CH), 129.47 (CH), 139.39 (CH) and 157.12 (C), m/z [EI] 402 (8%, M^+ (^{127}I)), 220 (49), 203 (10), 183 (100), 155 (10), 106 (7), 93 (10), 92 (10) and 76 (11). [Found: M^+ , 401.8937. $\text{C}_{10}\text{H}_{12}^{127}\text{I}_2\text{O}$ requires M , 401.8977].

1-Iodo-5-(2'-iodophenoxy)pentane (707)



Using tetrahydropyran as the solvent in the general procedure, treatment of 1-aminobenzotriazole (204) (50 mg, 0.4 mmol) with NIS (210 mg, 1 mmol) furnished the *title compound* (707) (34 mg, 24%) as an orange brown oil, ν_{\max} 3002, 2944, 2876, 1644, 1582, 1479, 1465, 1439, 1162, 1122, 1051, 1018, 980, 908, 865 and 650 cm^{-1} , δ_{H} (250 MHz) 2.14-2.51 (6H, m, 2-, 3- & 4-CH₂), 3.74 (2H, t, J 7.0, 1-CH₂), 4.52 (2H, t, J 6.1, 5-CH₂), 6.80 (1H, dd, J 7.7 and 1.0, 6'-H), 7.27 (1H, dd, J 7.7, 7.7, 5'-H), 7.29 (1H, dd, J 7.7, 7.7, 4'-H) and 7.77 (1H, dd, J 7.7, 1.0, 3'-H), δ_{C} (68 MHz) 6.81 (CH₂), 27.84 (CH₂), 28.02 (CH₂), 33.12 (CH₂), 68.68 (CH₂), 85.12 (C-I), 111.99 (CH), 122.43 (CH), 129.38 (CH), 139.39 (CH) and 153.14 (C), m/z [EI] 416 (26%, M^+ (^{127}I)), 220 (100), 197 (65), 162 (11), 106 (8), 92 (10), 76 (8) and 69 (69). [Found: M^+ , 415.9117. $\text{C}_{11}\text{H}_{14}^{127}\text{I}_2\text{O}$ requires M , 415.9134].

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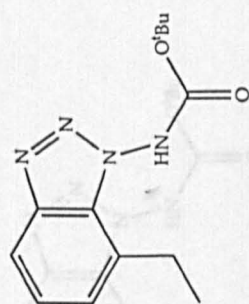
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- - -

APPENDIX



(571)

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 LR 3.000
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 CY 55.00
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 E2 23499.32H
 F2 -499.20H
 HZ/CM 635.636
 PPM/CM 6.315
 SR -6135.62

100.011
 79.0
 50.0
 37.0
 36.0
 35.0
 34.0
 33.0
 32.0
 31.0
 30.0
 29.0
 28.0
 27.0
 26.0
 25.0
 24.0
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Figure 4

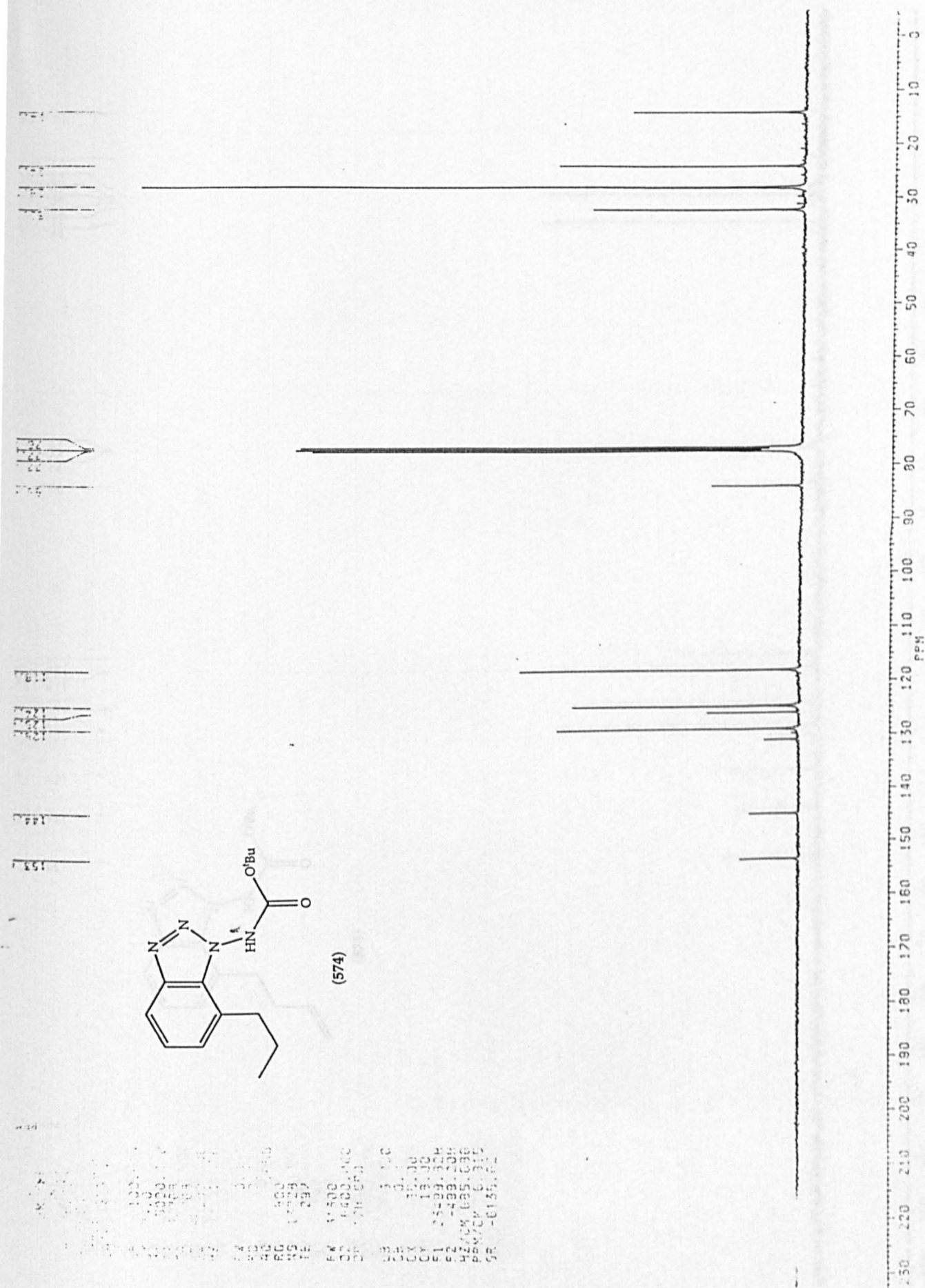
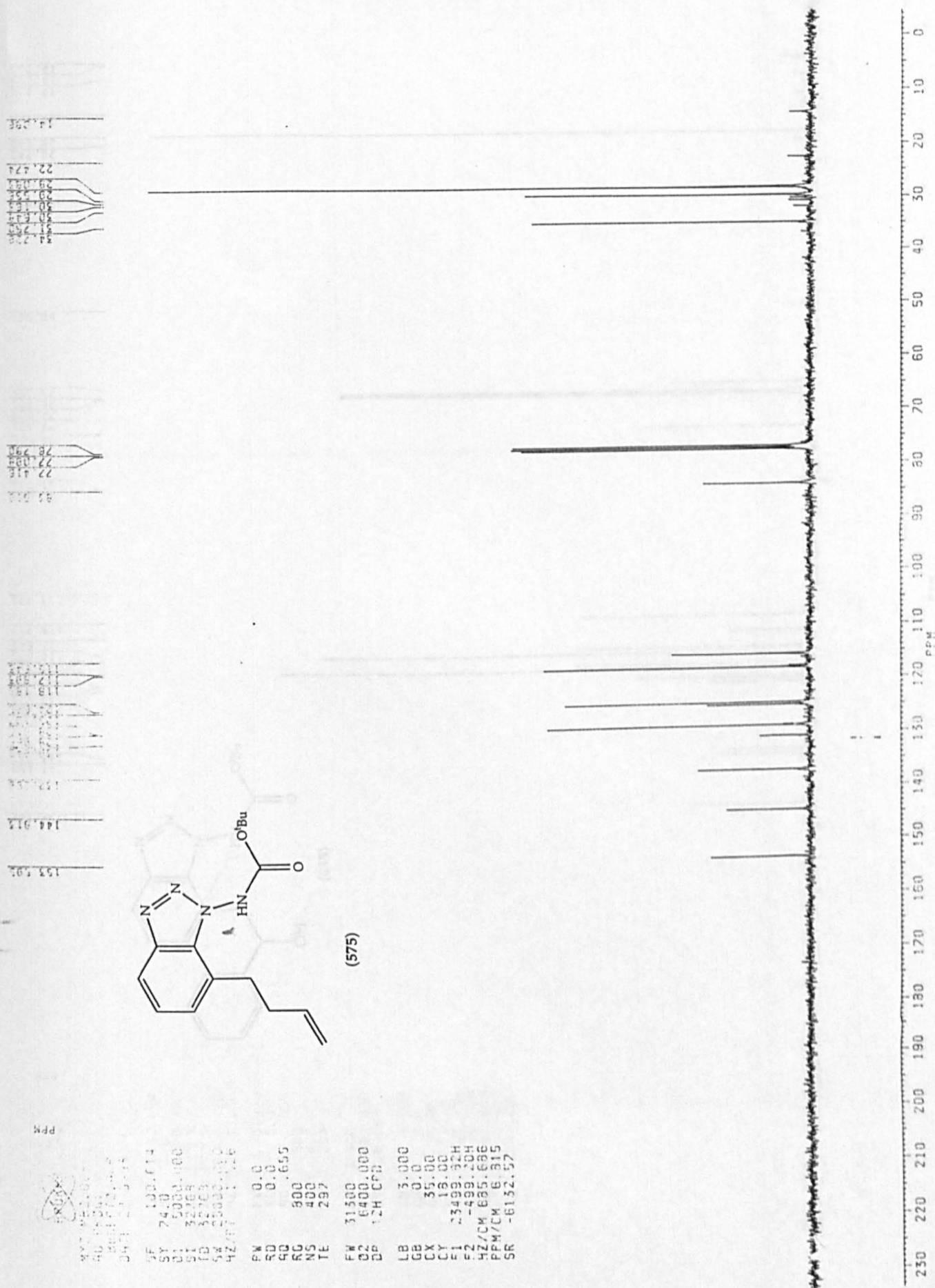


Figure 5



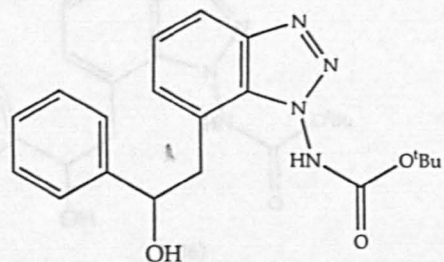
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 S1 52.068
 TD 52.068
 G4 25000.000
 HZ/PT 1.520

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 RD 0.0
 AQ .655
 RG 800
 NS 400
 TE 297

FW 31500
 D2 6400.000
 DP 12H CPD

LB 3.000
 GB 0.0
 CX 35.00
 CY 18.00
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 PPM/CM 6.815
 SR -6132.57



(635)

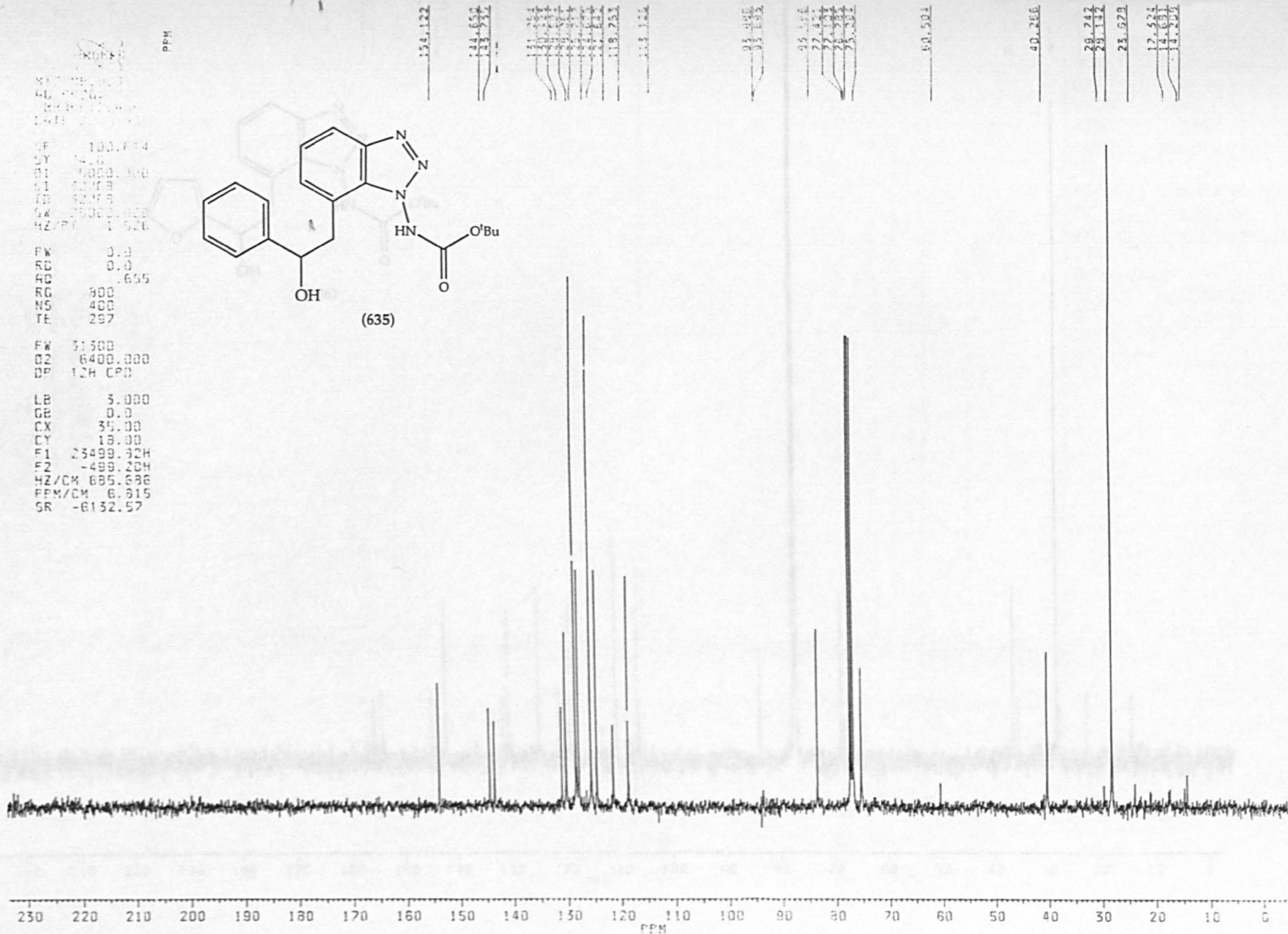
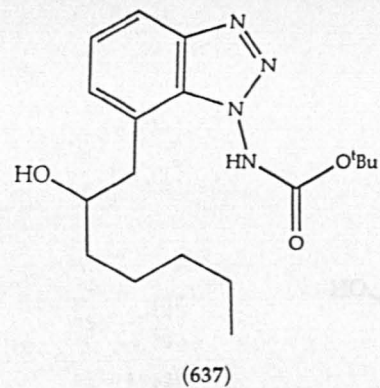


Figure 7

MAB308



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OBNUC 13C
EXMOD BCM
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OBSET 135.00 kHz
OBFIN 5200.0 Hz
POINT 32768
FREQU 20000.0 Hz
SCANS 301
ACQTM 0.819 sec
PD 2.181 sec
PW1 3.8 us
IRNUC 1H
SLVNT CDCL3
EXREF 77.00 ppm
BF 1.50 Hz
RGAIN 27
OPERATOR : _____

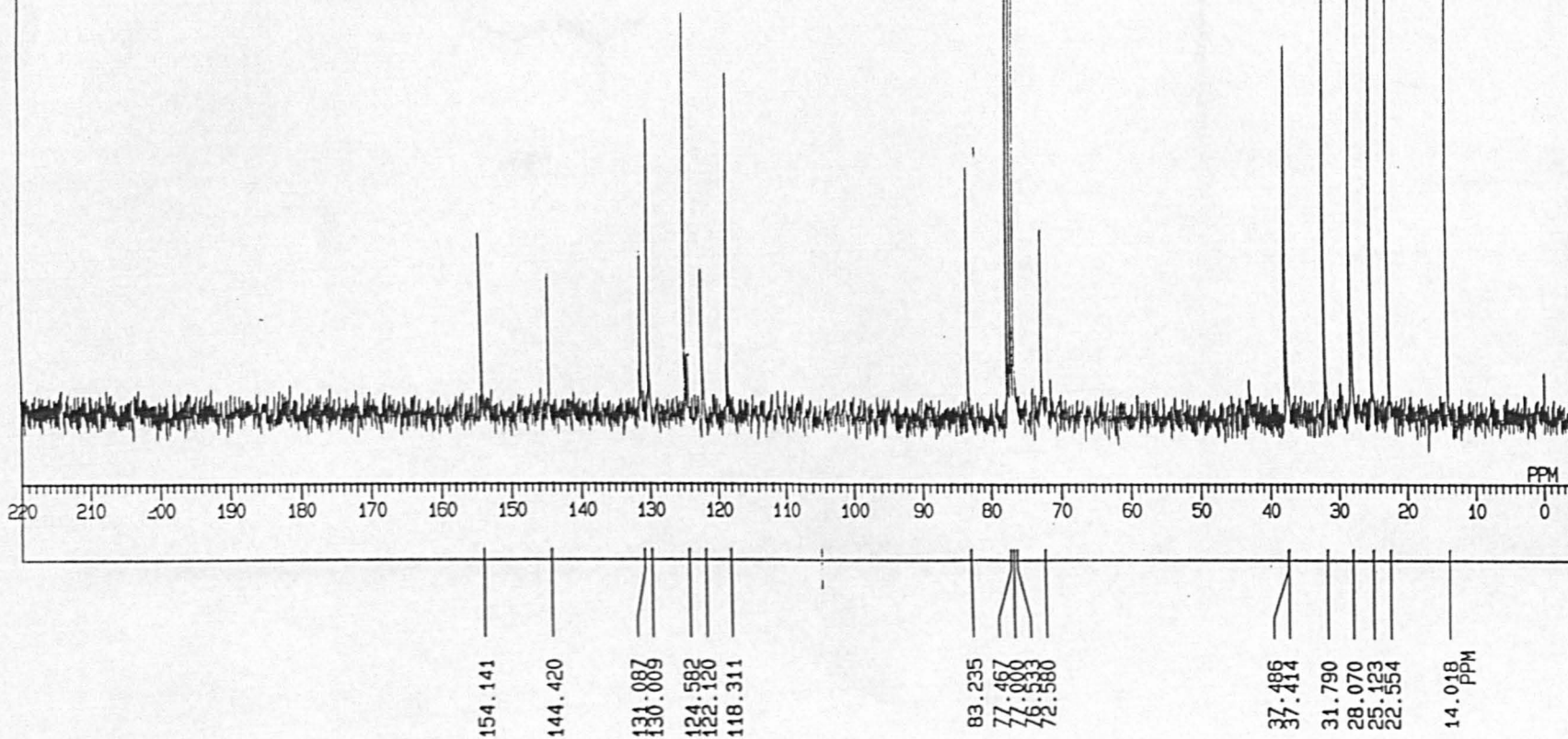
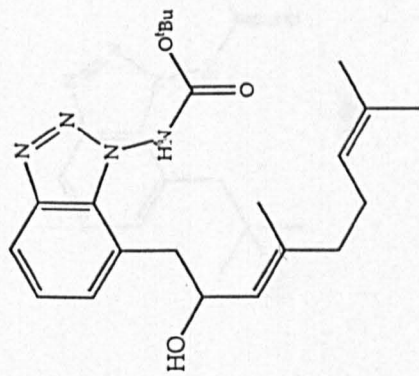


Figure 9



(638)

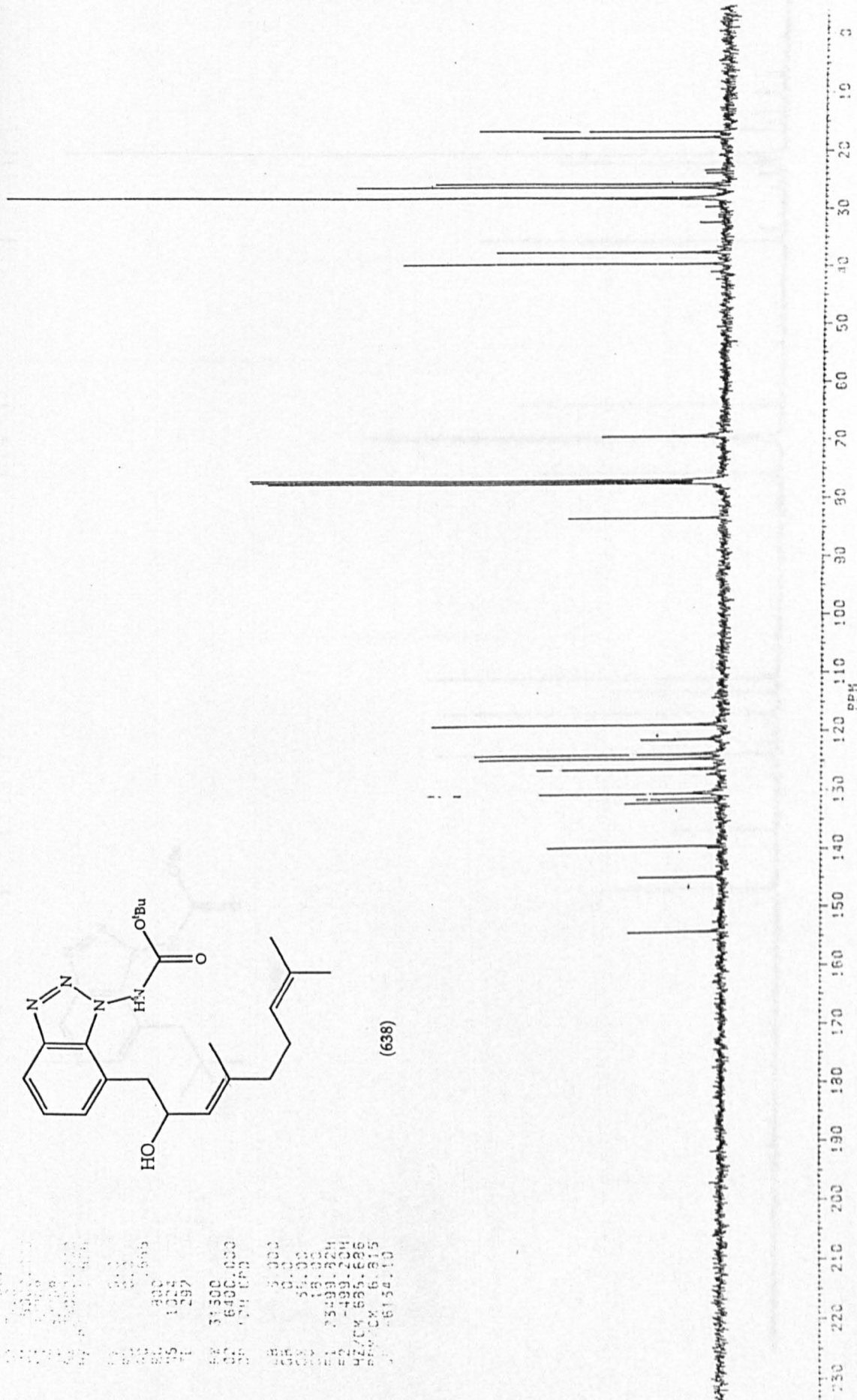
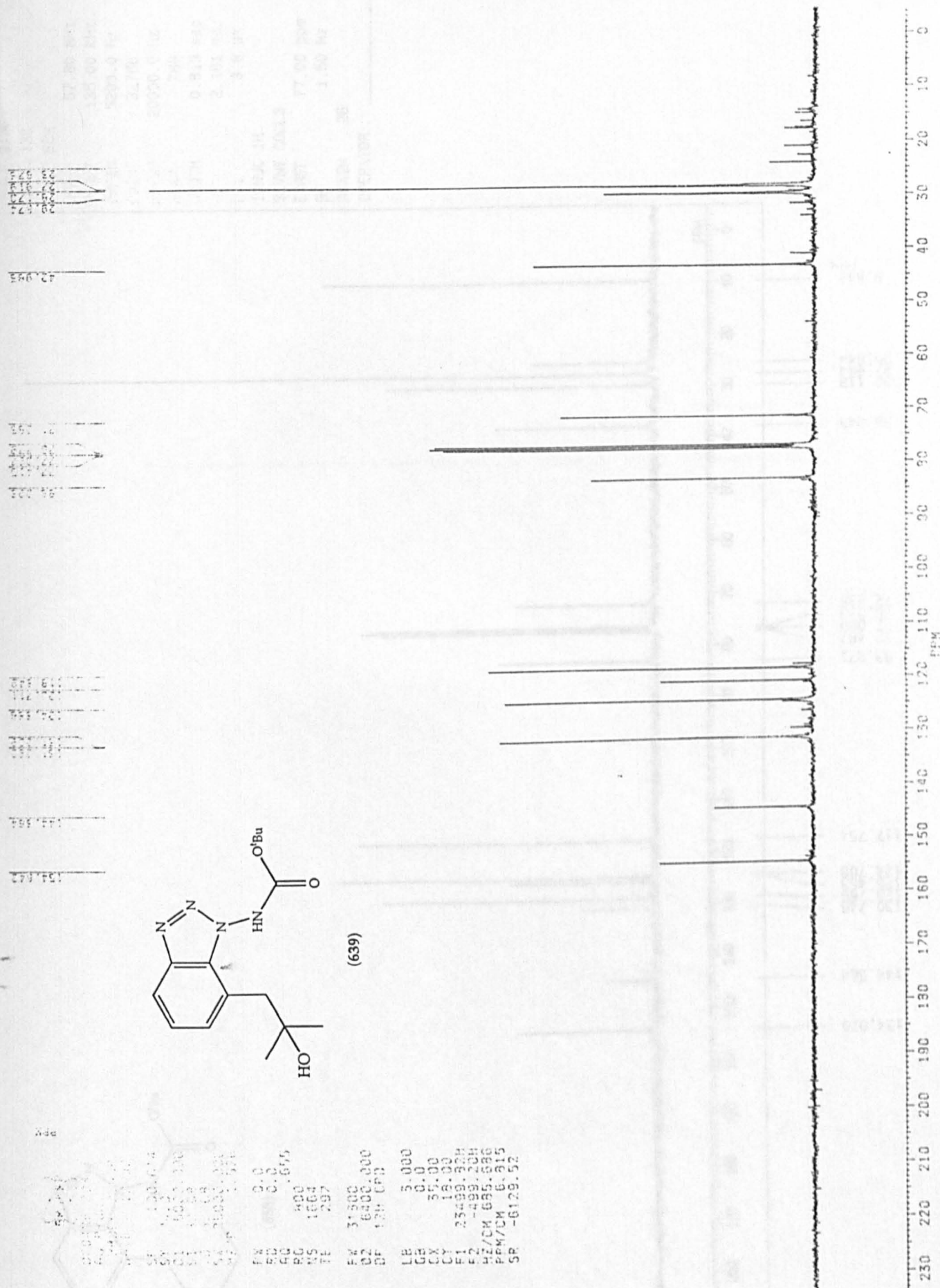
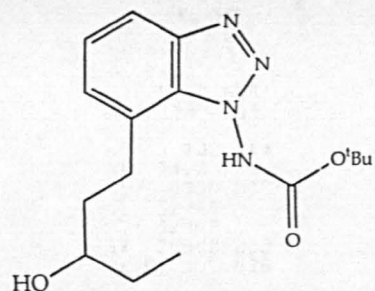


Figure 10



MAB301



(658)

02-SEP-92 14:06:29
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FIDLE 13C
EXMOD BCM
FIDR 67.80 MHz
ORBIT 135.00 kHz
ORFIN 5200.0 Hz
POINT 32768
PACED 20000.0 Hz
PACED 788
ACQTH 0.819 sec
PACED 2.181 sec
PACED 3.8 us
IRNUC 1H
SLVNT CDCL3
EXREF 77.00 ppm
BF 1.50 Hz
RGAIN 26
OPERATOR : _____

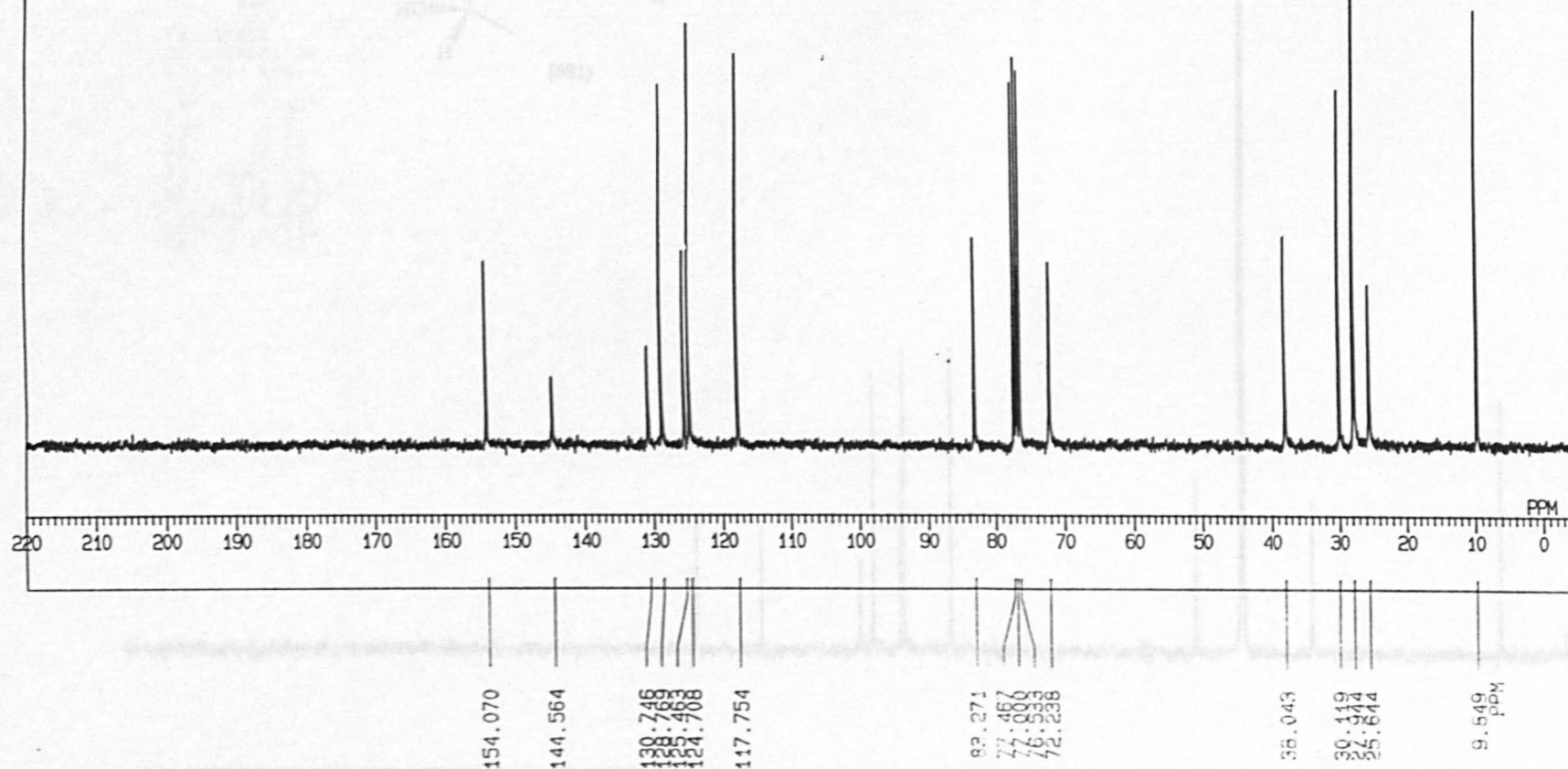


Figure 12

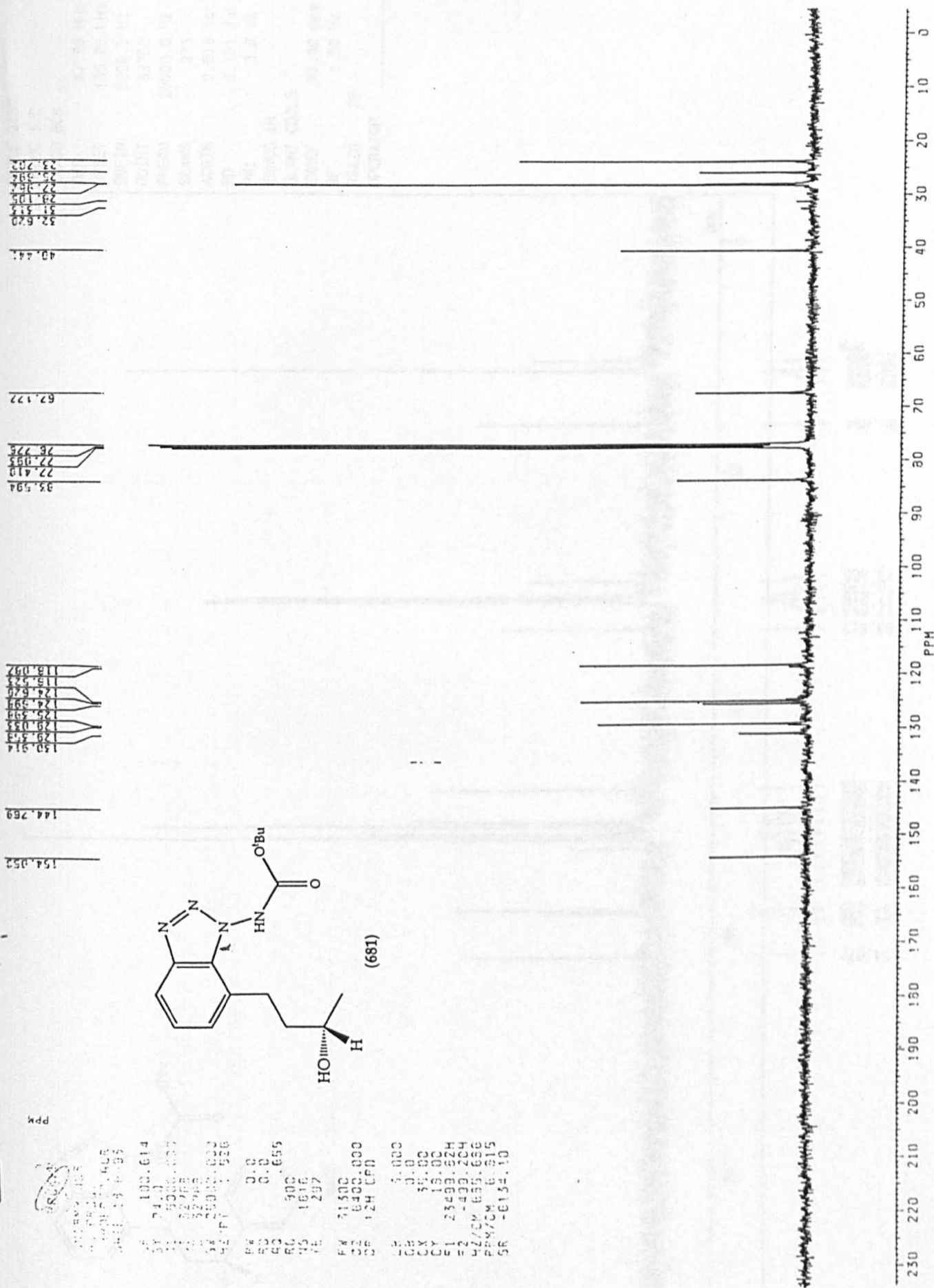
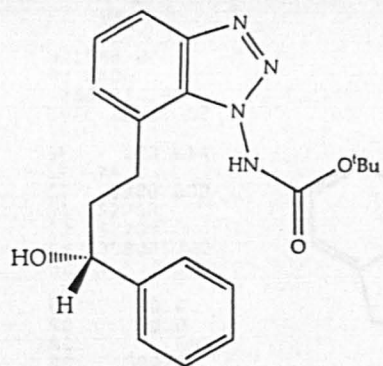
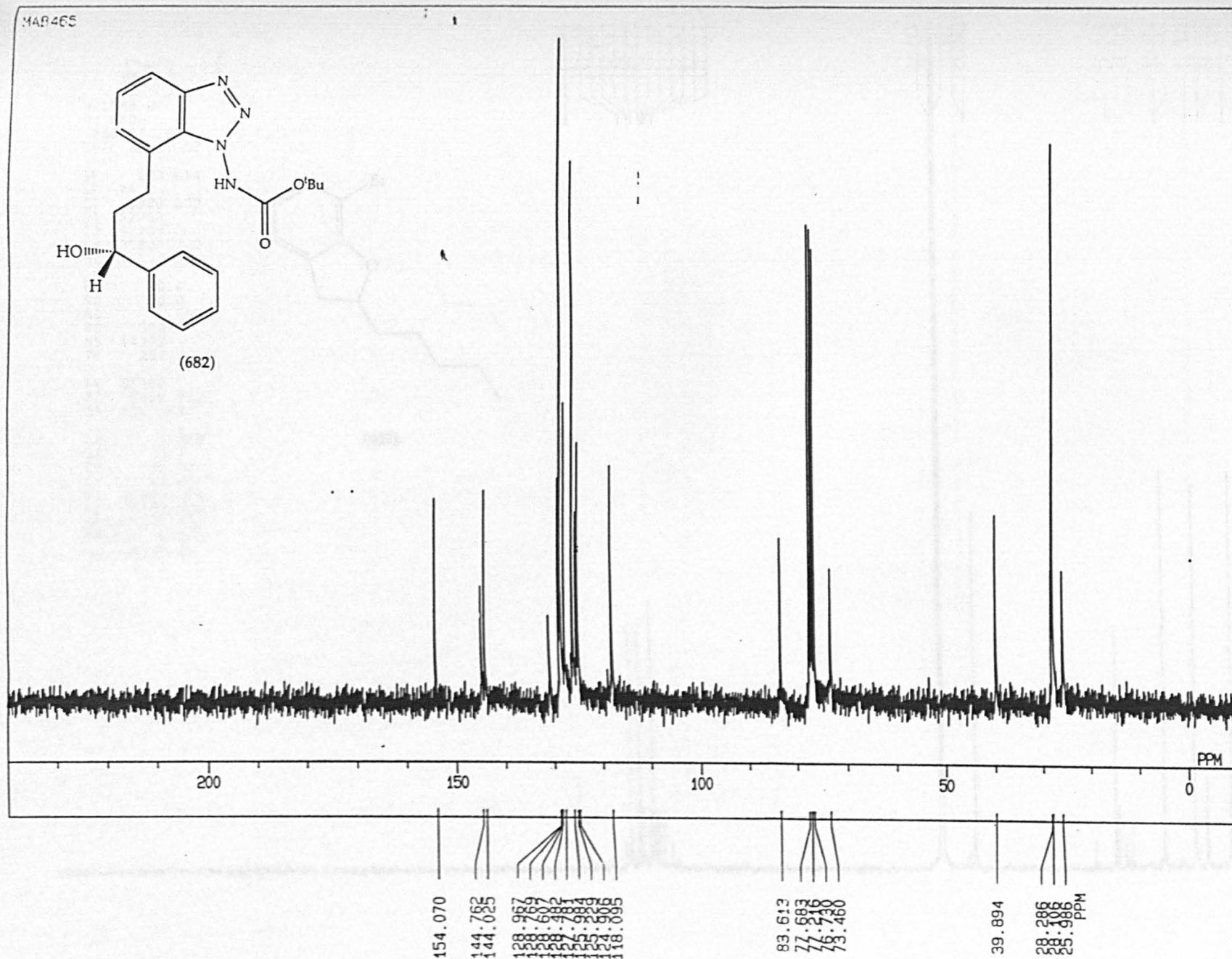


Figure 13



(682)



```

23-JUN-93 10:51:35
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EXMOD BCM
OFR 67.80 MHz
OBSET 135.00 kHz
OBFIN 5200.0 Hz
POINT 32768
FREQU 20000.0 Hz
SCANS 278
ACQTM 0.819 sec
PD 2.181 sec
PW1 3.8 us
IRNUC 1H
SLVNT CDCL3
EXREF 77.00 ppm
BF 1.50 Hz
RGAIN 26
OPERATOR :

```

Figure 14

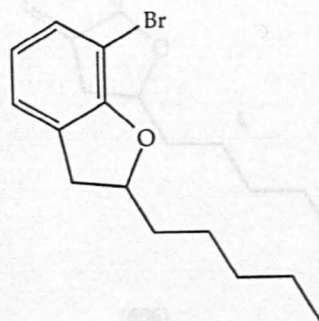
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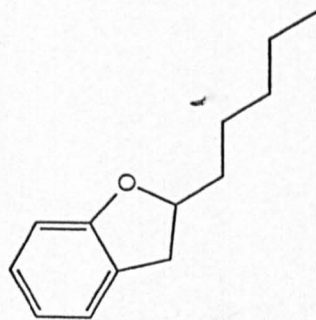
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70	32768
94	25000.000
42/PT	1.526

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RD	0.0
AQ	.655
RG	300
NS	14272
TE	292

FW 31300
02 6400.000
CP 12H CPD

LB	3.000
GB	0.0
CX	35.00
CY	12.00
F1	23499.32H
F2	-499.20H
HZ/CM	635.636
PPM/CM	6.315
SR	-6135.62





(656)

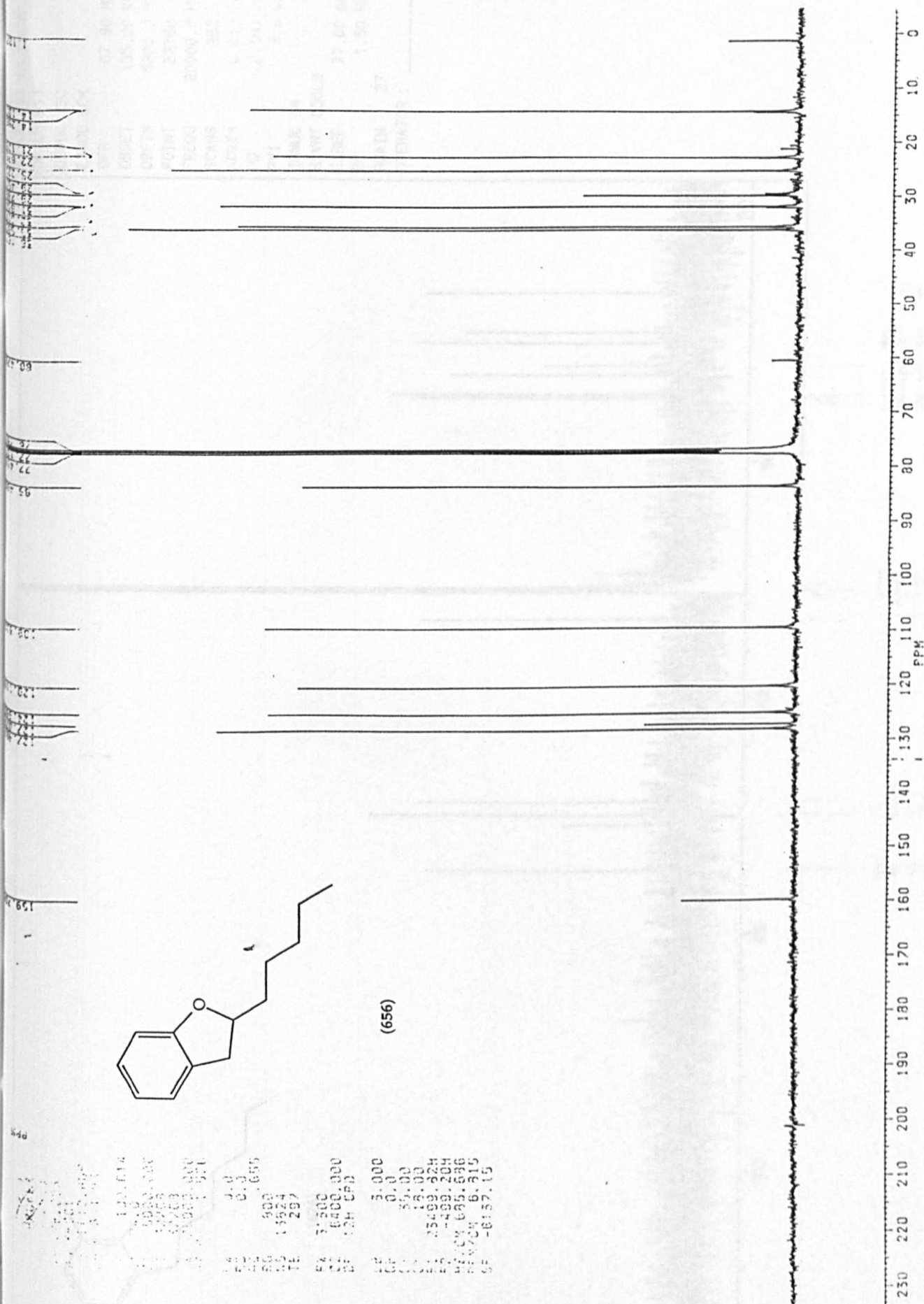
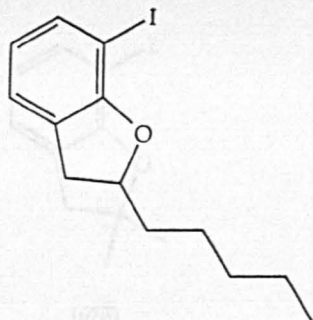


Figure 16



(676)

01-JUL-93 13:19:30
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 OBSET 135.00 KHz
 OBFIN 5200.0 Hz
 POINT 32768
 FREQU 20000.0 Hz
 SCANS 268
 ACQTM 0.810 sec
 PD 2.141 sec
 PW1 3.8 sec
 IRNUC 1H
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 1.50 Hz
 RGAIN 27
 OPERATOR : _____

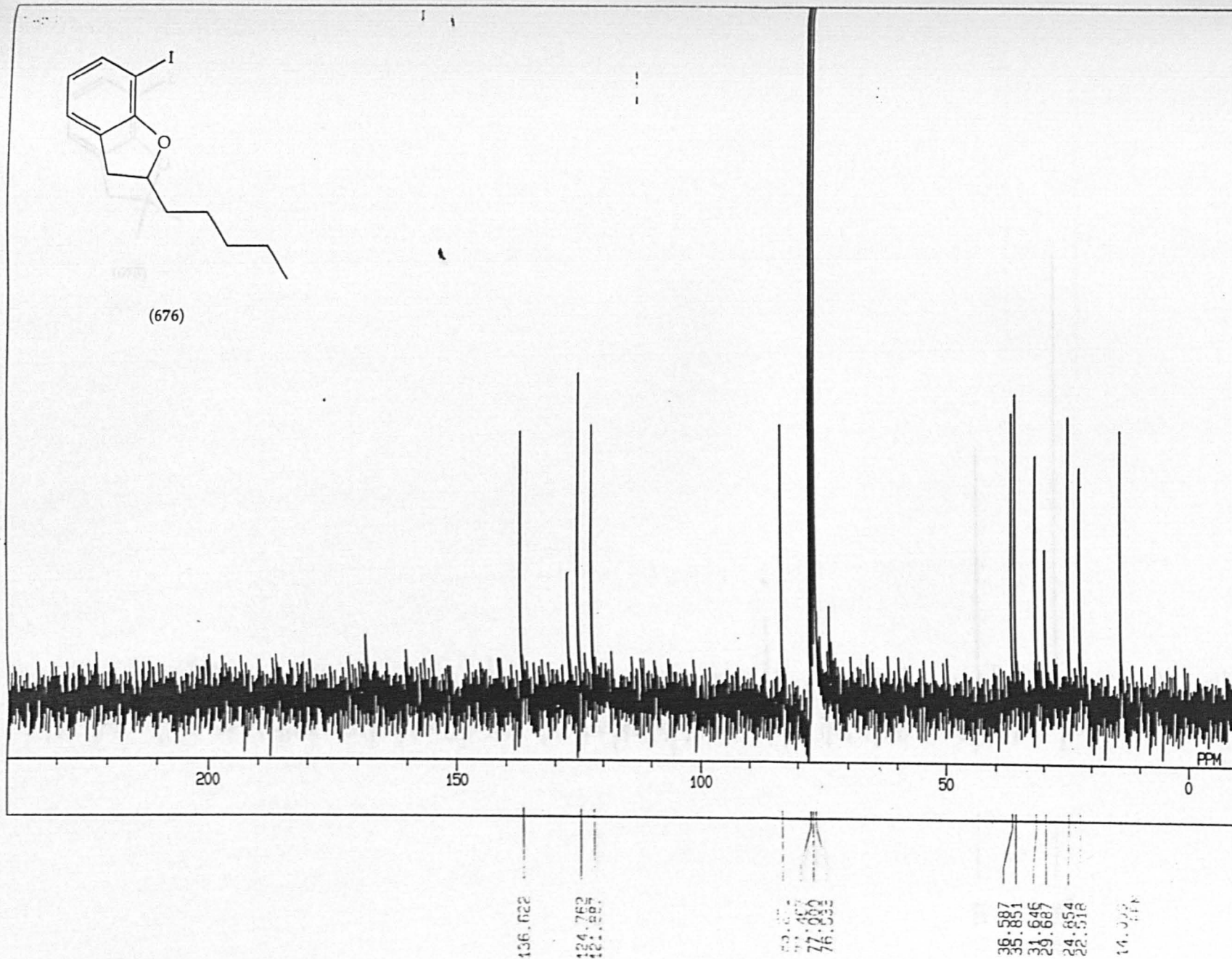


Figure 17

04-JUL-93 22:03:27

100% 3100

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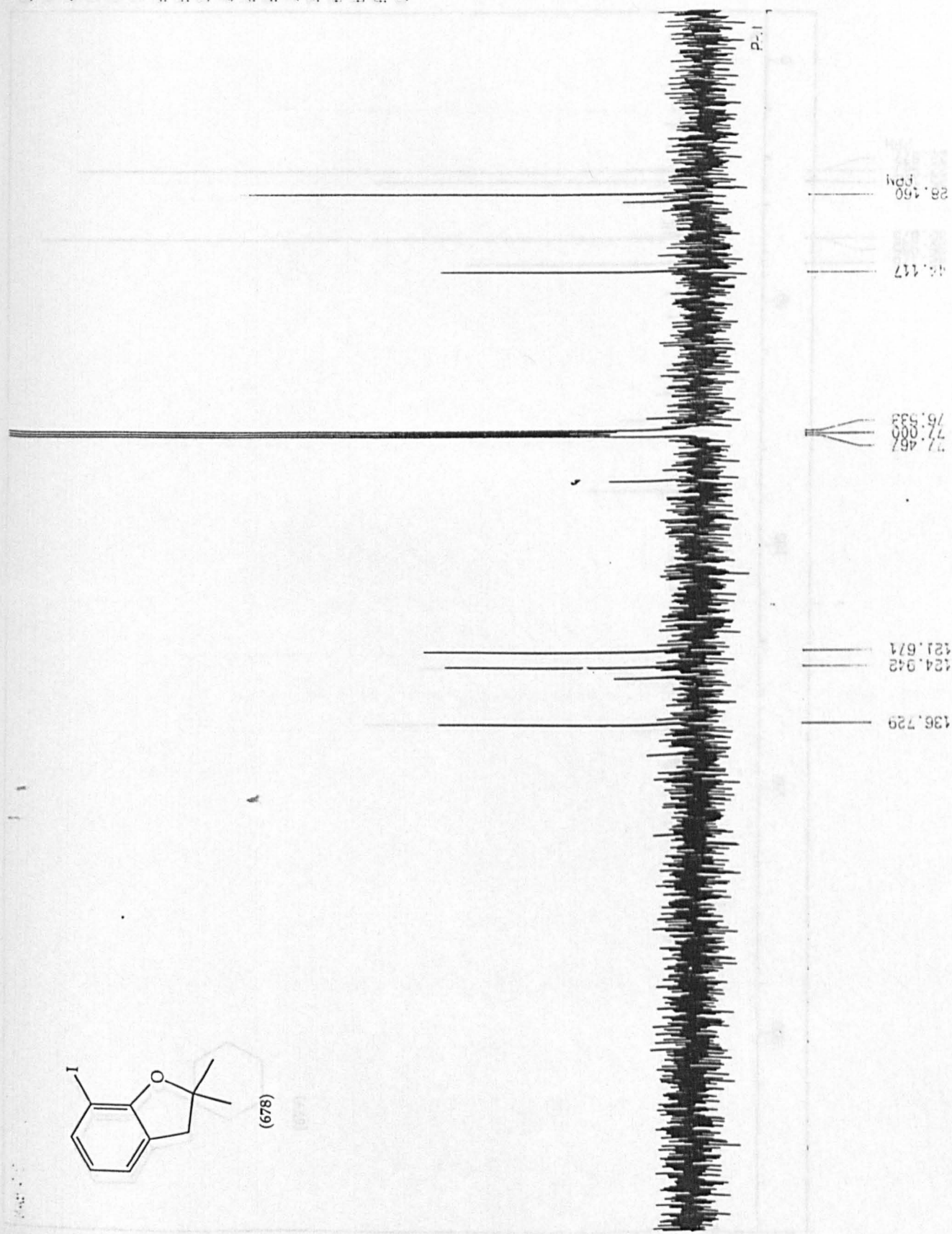
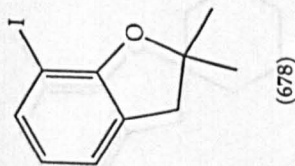
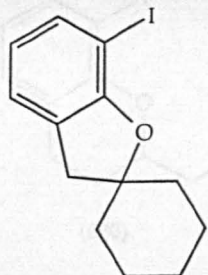


Figure 18

MAB



(679)

25-JUL-93 14:19:29
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OBNUC 13C
EXMOD BCM
OFR 67.80 MHz
OBSET 135.00 kHz
OBFIN 5200.0 Hz
POINT 32768
FREQU 20000.0 Hz
SCANS 400
ACQTM 0.819 sec
PD 2.181 sec
PW1 3.8 us
IRNUC 1H
SLVNT CDCL3
EXREF 77.00 ppm
BF 1.50 Hz
RGAIN 27
OPERATOR : _____

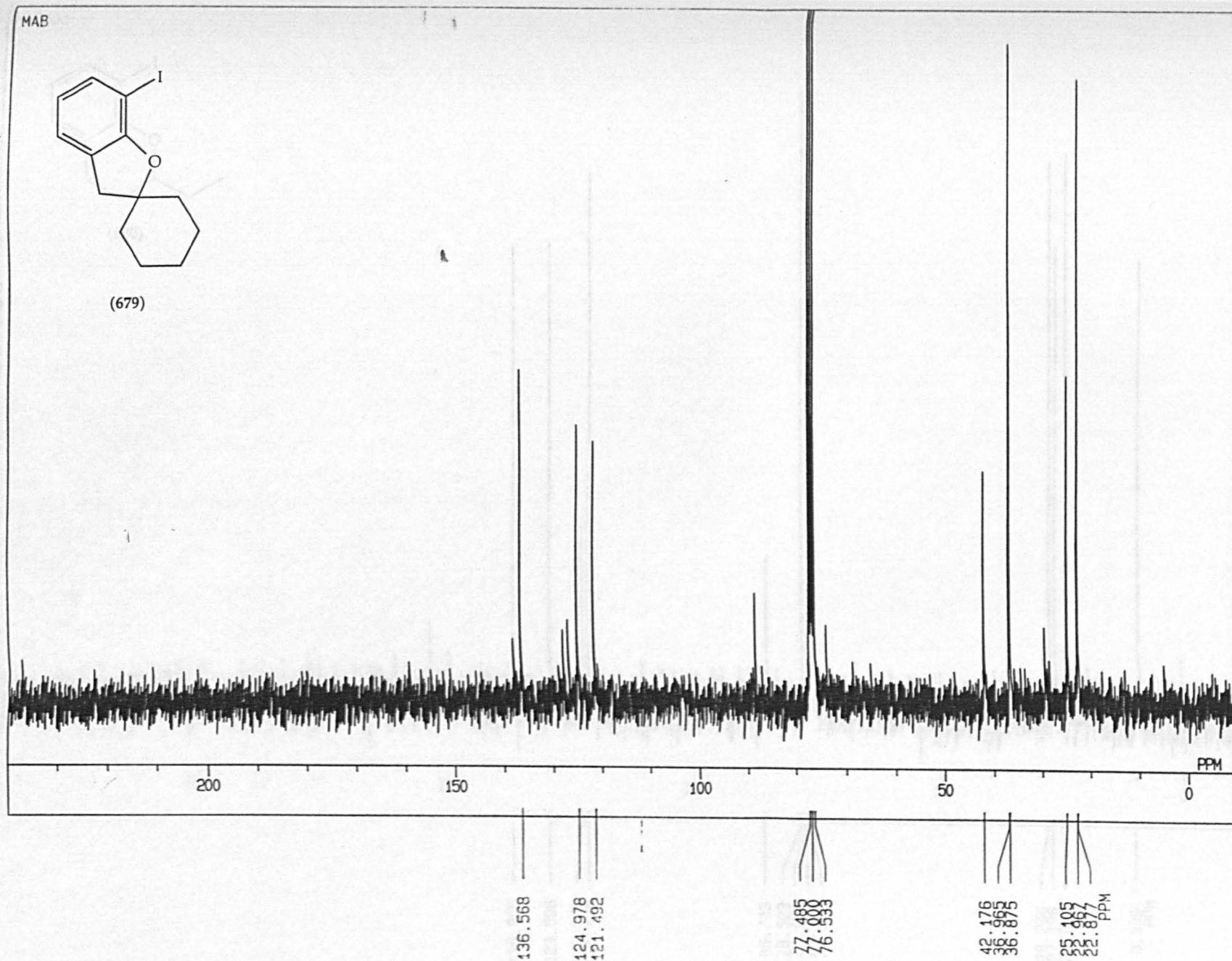


Figure 19

24-JUL-93 18:30:25

OFIL Q12C

ORNUC 1H

EXMOD BCM

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OBSET 135.00 kHz

ORFIN 5200.0 Hz

POINT 32763

FREQU 20000.0 Hz

SCANS 400

ACQTM 0.819 sec

PD 2.181 sec

PW1 3.8 us

IRNUC 1H

SLVNT CDCL3

EXREF 77.00 ppm

BF 1.50 Hz

RGAIN 28

OPERATOR :

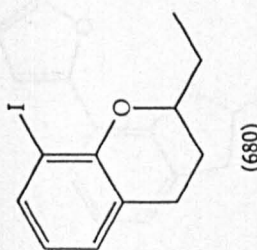
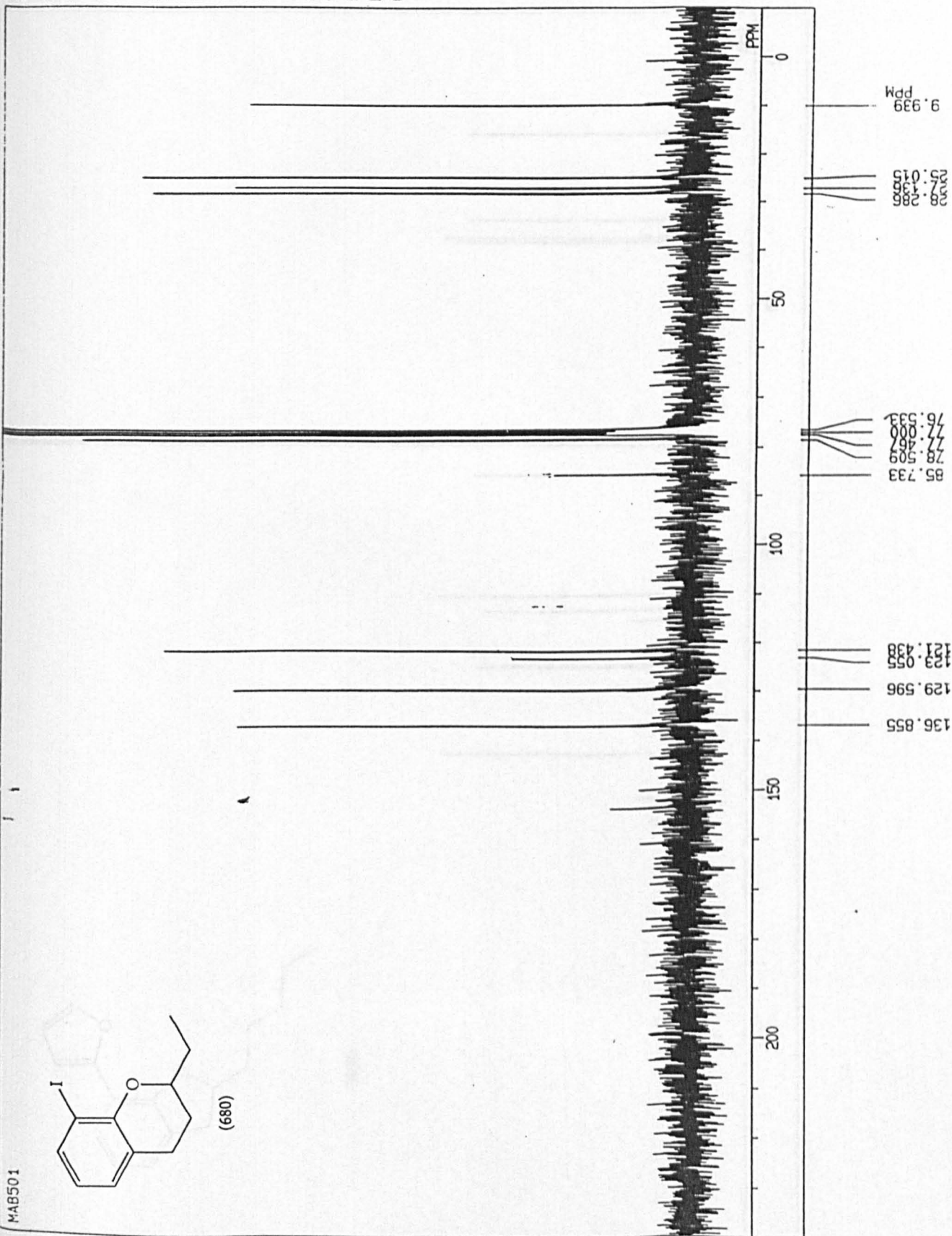


Figure 20

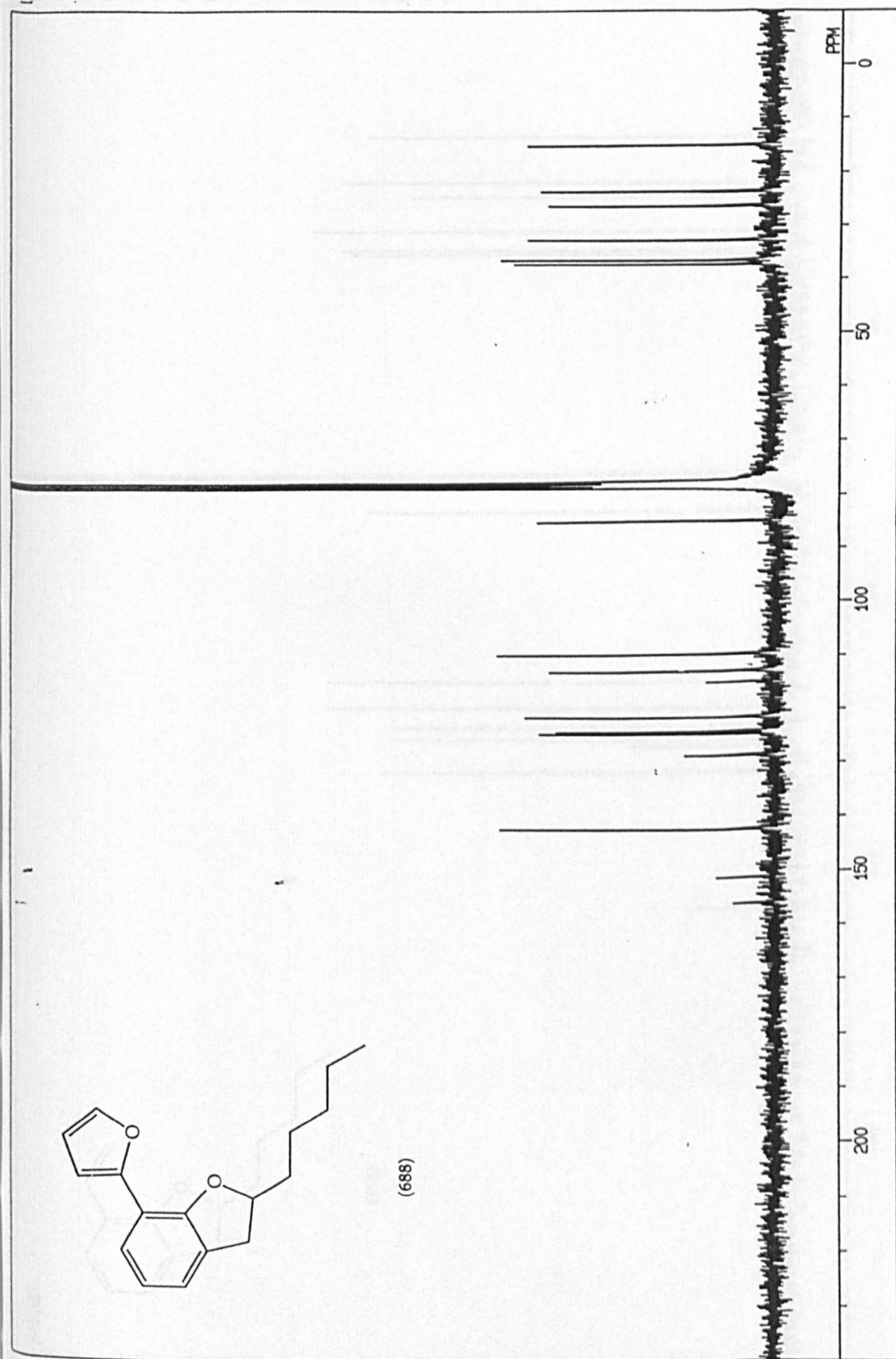
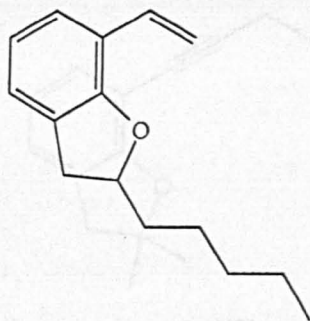


Figure 21

MAB537



(690)

29-SEP-93 13:15:14

DFILE Q13C

OBNUC 13C

EXMOD BCM

OFR 67.80 MHz

OBSET 135.00 kHz

OBFIN 5200.0 Hz

POINT 32768

FREQU 20000.0 Hz

SCANS 926

ACQTM 0.819 sec

PD 2.181 sec

PW1 3.8 us

IRNUC 1H

SLVNT CDCL3

EXREF 77.00 ppm

BF 1.50 Hz

RGAIN 27

OPERATOR : _____

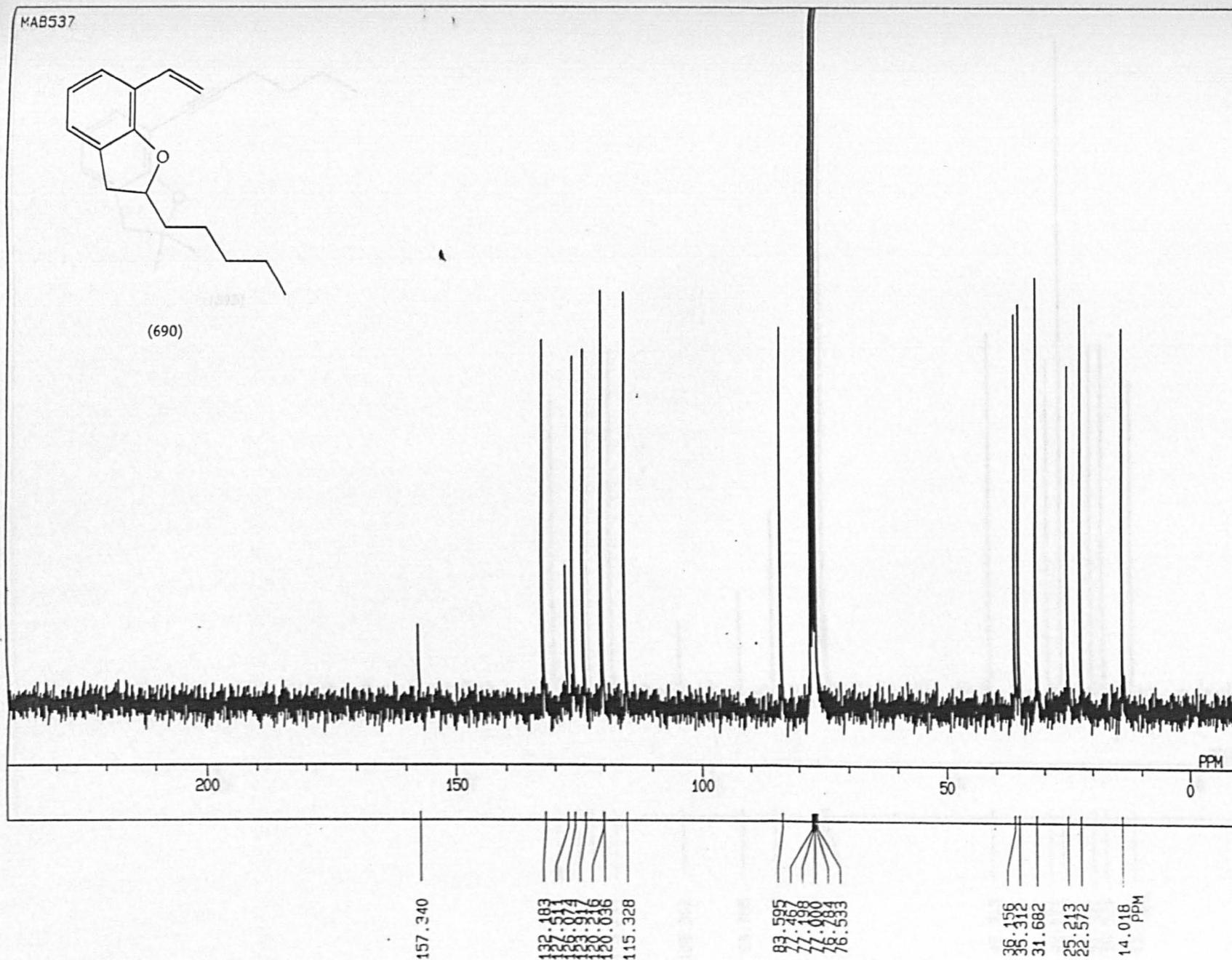


Figure 22

MAB536

29-SEP-93 11:23:17

DFILE Q13C

OBNUC 13C

EXMOD BCM

OFR 67.80 MHz

OBSET 135.00 kHz

OBFIN 5200.0 Hz

POINT 32768

FREQU 20000.0 Hz

SCANS 800

ACQTM 0.819 sec

PD 2.181 sec

PW1 3.8 us

IRNUC 1H

SLVNT CDCL3

EXREF 77.00 ppm

BF 1.50 Hz

RGAIN 27

OPERATOR : _____

(693)

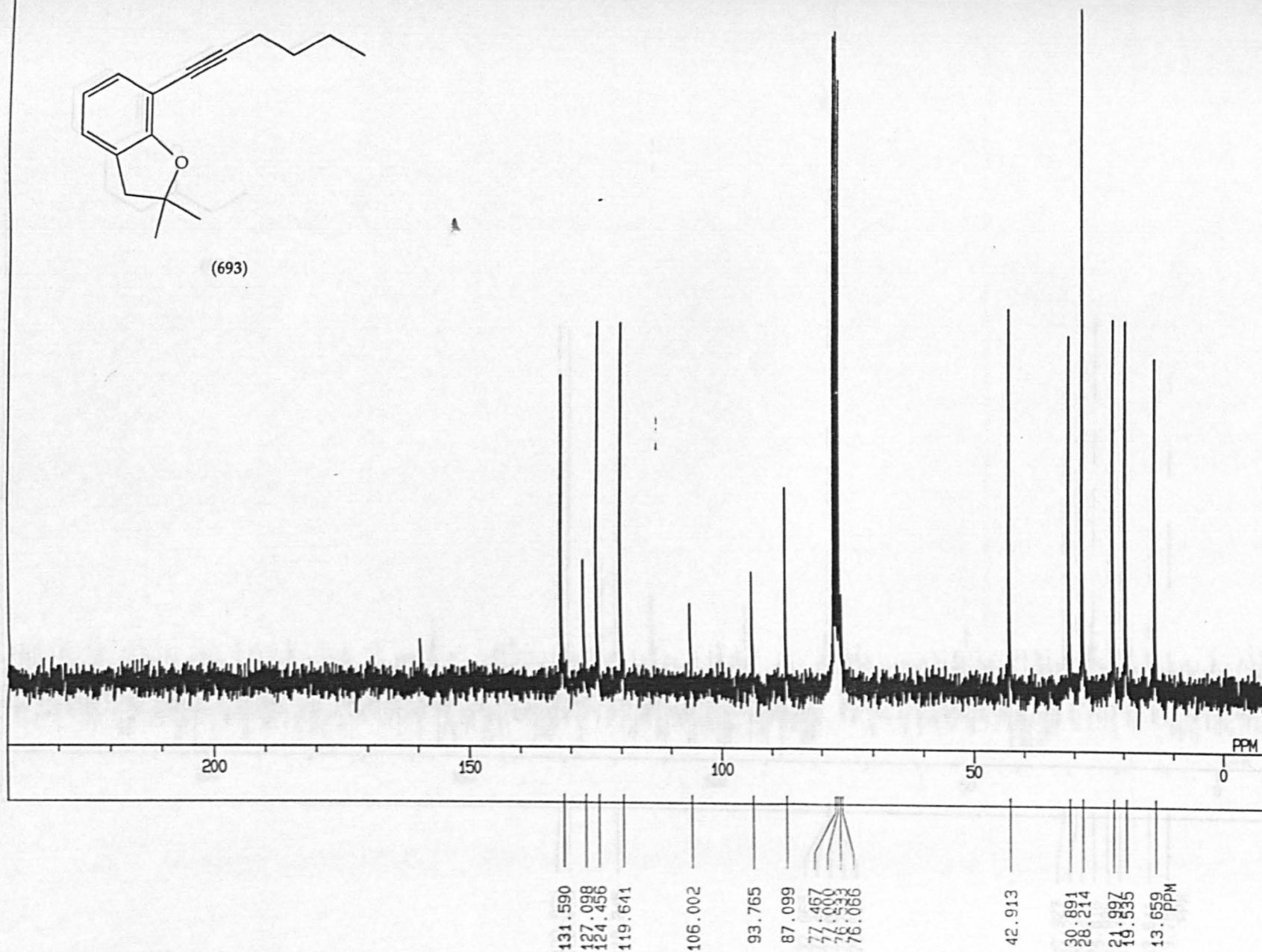
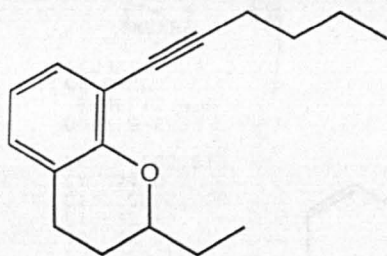


Figure 23

MAB531



(694)

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 EXMOD BCM
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 FREQU 20000.0 Hz
 SCANS 1205
 ACQTM 0.819 sec
 PD 2.181 sec
 PW1 3.8 us
 IRNUC 1H
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 1.50 Hz
 RGAIN 27
 OPERATOR : _____

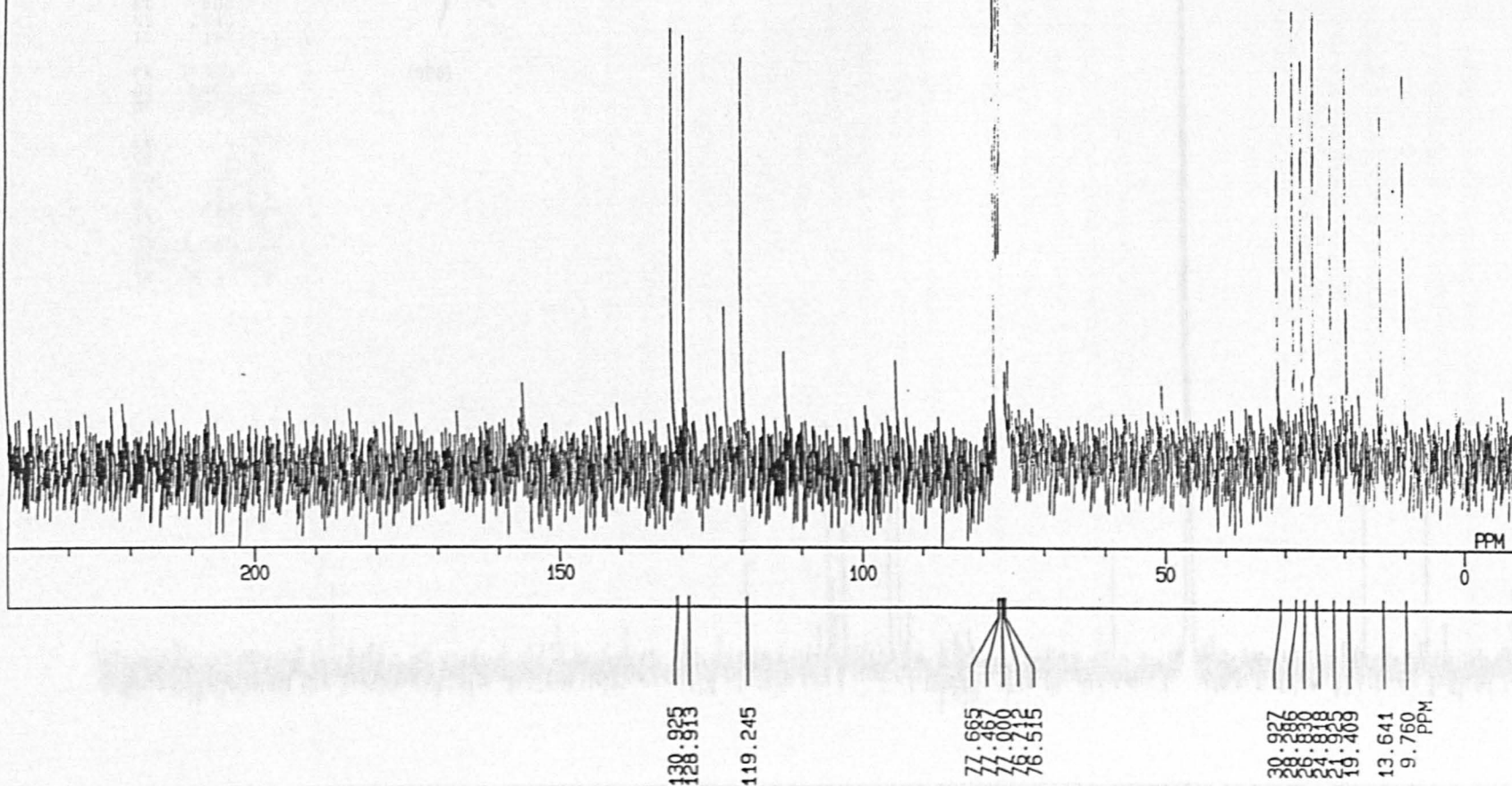


Figure 24

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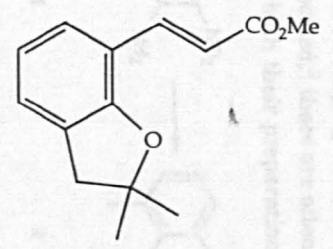
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 HZ/PT 1.521

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 RG 800
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 TE 297

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 O2 6400.000
 DP 12H CPO

LB 3.000
 GB 0.0
 CX 35.00
 CY 12.00
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PPM
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(696)

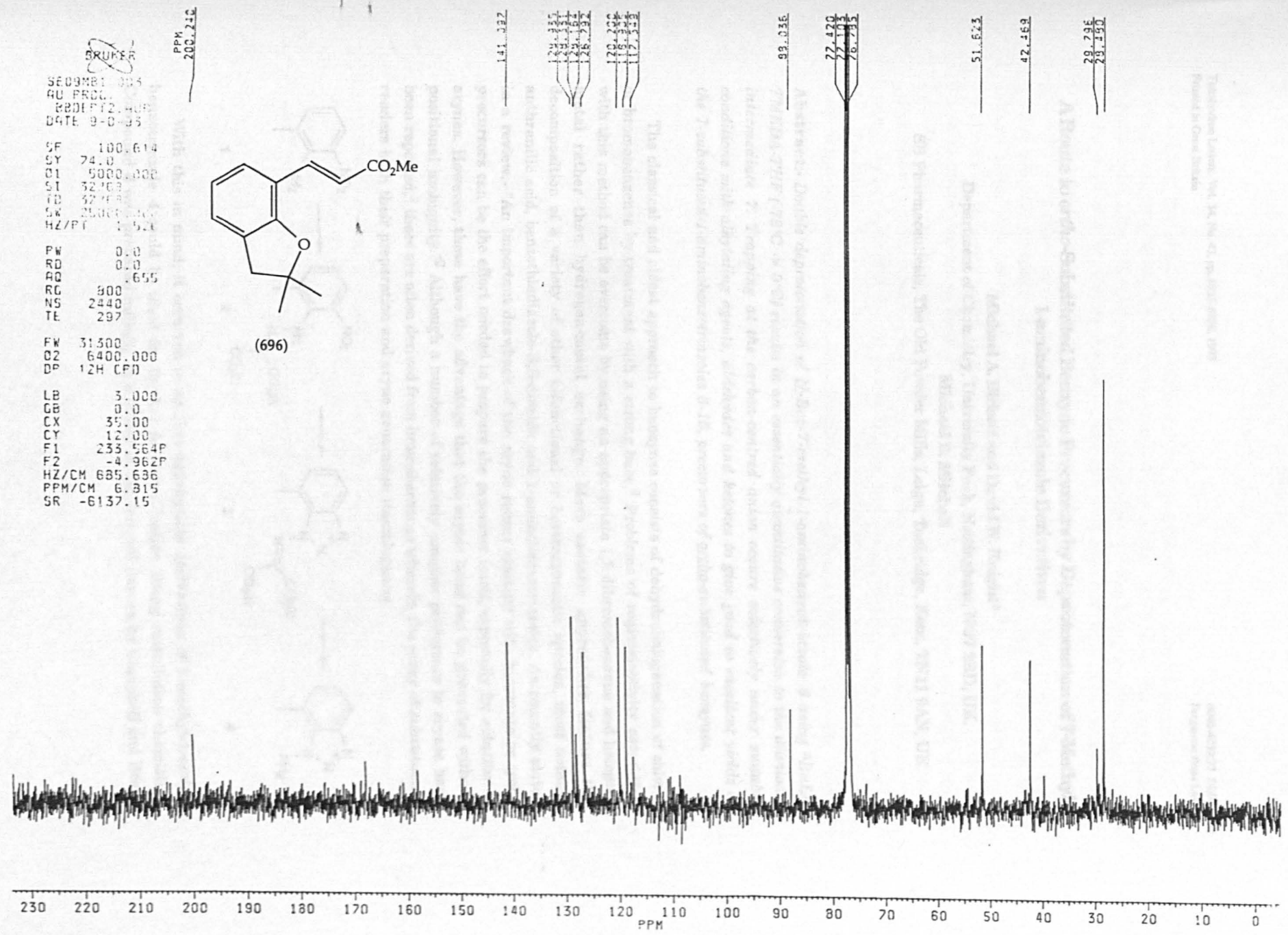


Figure 25

A Route to *ortho*-Substituted Benzyne Precursors by Deprotonation of 7-Methyl-1-aminobenzotriazole Derivatives

Michael A. Birkett and David W. Knight*

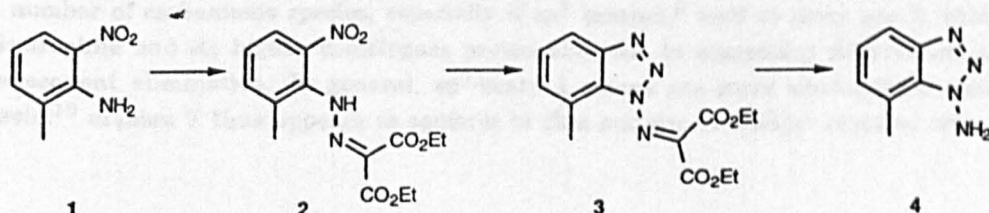
Department of Chemistry, University Park, Nottingham, NG7 2RD, UK.

Michael B. Mitchell

SB Pharmaceuticals, The Old Powder Mills, Leigh, Tonbridge, Kent, TN11 9AN, UK.

Abstract: Double deprotonation of *N*-Boc-7-methyl-1-aminobenzotriazole **6** using $n\text{BuLi}$ -TMEDA-THF [$-78^\circ\text{C} \rightarrow 0^\circ\text{C}$] results in an essentially quantitative conversion to the dianionic intermediate **7**. Trapping at the carbon-centred anion occurs selectively under suitable conditions with alkylating agents, aldehydes and ketones to give good to excellent yields of the 7-substituted-1-aminobenzotriazoles **8-15**, precursors of *ortho*-substituted benzyne.

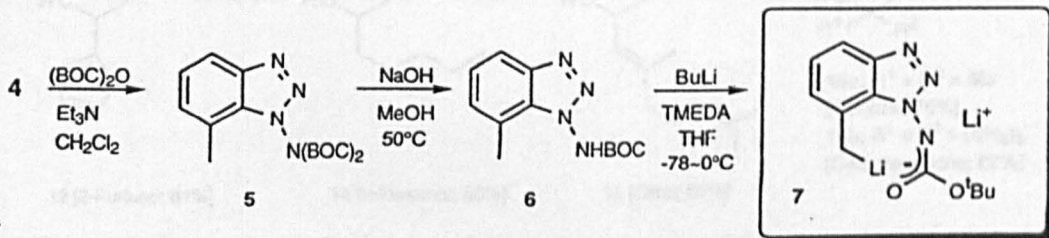
The classical and oldest approach to benzyne consists of dehydrohalogenation of chloro- or bromobenzenes by treatment with a strong base.¹ Problems of regioselectivity associated with this method can be overcome by using an appropriate 1,2-dibromobenzene and halogen-metal rather than hydrogen-metal exchange. More esoteric approaches feature the decomposition of a variety of other bifunctional or heteroaromatic species, most notably anthranilic acid, benzothiadiazole-S,S-dioxide and 1-aminobenzotriazoles. As recently stated in a review: "An important drawback of the aryne routes starting with bidentate or cyclic precursors can be the effort needed to prepare the precursor itself, especially for substituted arynes. However, these have the advantage that the arynic bond can be generated without positional ambiguity."² Although a number of relatively complex precursors to arynes have been reported,³ these are often derived from bromobenzenes wherein the array of substituents renders both their preparation and aryne generation unambiguous.



With this in mind, it occurred to us that appropriate derivatives of 7-methyl-1-aminobenzotriazole **4** could be ideal for further functionalisation using metallation chemistry. Compound **4** was prepared initially as outlined in the seminal papers by Campbell and Rees⁴

describing the generation of benzyne from 1-aminobenzotriazoles, under notably mild conditions, using either lead(IV) acetate or *N*-bromosuccinimide.⁴ Thus, the amino group in commercial 2-methyl-6-nitroaniline **1** was diazotised and the resulting diazonium species trapped *in situ* by diethyl malonate. The resulting adduct **2** was then reduced to the corresponding aniline; however, in our hands, the original procedure [10% Pd-C, H₂, MeOH]⁴ gave relatively poor yields of rather impure material. These were much improved by using transfer hydrogenation [10% Pd-C, cyclohexene, EtOH, reflux, 2-3h].⁵ A second diazotisation then led smoothly to the benzotriazole **3** and finally to the required amino derivative **4**, following hydrolysis using 6M HCl but with methanol as co-solvent, rather than neat as in the original method.⁴ The amino function in the heterocycle **4** appeared to be well positioned to facilitate deprotonation of the adjacent methyl group, after appropriate derivatisation.⁶ We chose to use a *t*butoxycarbonyl function for this purpose, both because it would not be expected to undergo deprotonation⁷ and because it should be easy to remove.

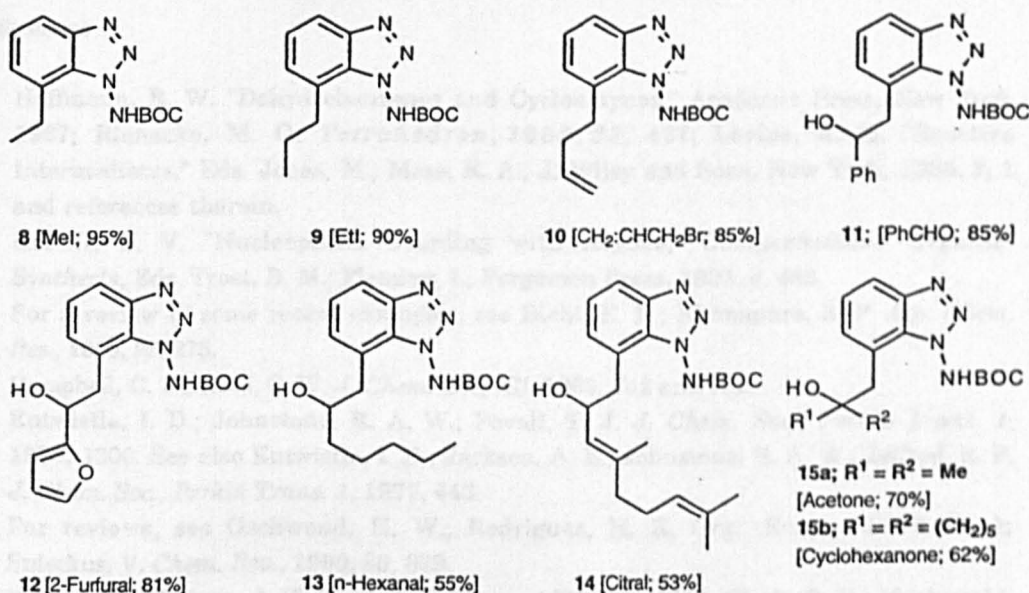
Treatment of the benzotriazole **4** with (BOC)₂O [Et₃N, DMAP, CH₂Cl₂, 0~20°C, 4~5h] led not to the desired monoadduct **6** but rather to the *bis*-adduct **5** (89%); this was not a serious problem as one of these new groups could be removed in essentially quantitative yield by basic hydrolysis [NaOH, MeOH, 50°C, <1h]. After a number of trials, we found that the mono-BOC derivative **6** could be smoothly and essentially quantitatively deprotonated by exposure to 2.2 equivalents each of ⁿBuLi and TMEDA in THF initially at -78°C followed by warming to 0°C during 0.5h. The resulting dianionic species **7** decomposes at temperatures above 0°C.



Subsequent reactions with a range of electrophiles proceeded smoothly; the results are collected in the following Table.⁸ Alkylations were best carried out at -78°C using 1.1 equivalents of the electrophile; at higher temperatures, especially if an excess of the electrophile was used, competing *N*-alkylation became a serious problem. The 95% isolated yield of the adduct **8** from iodomethane indicates that the dianion **7** is formed in essentially quantitative yield. The excellent 90% return of adduct **9** from iodoethane is also significant as a number of carbanionic species, especially if sp² centred,⁹ tend to react poorly with this electrophile and its higher homologues presumably due to competing deprotonation and subsequent elimination. In general, sp³-centred anions are more nucleophilic and less basic;¹⁰ dianion **7** thus appears to conform to this pattern. A similar reaction with allyl

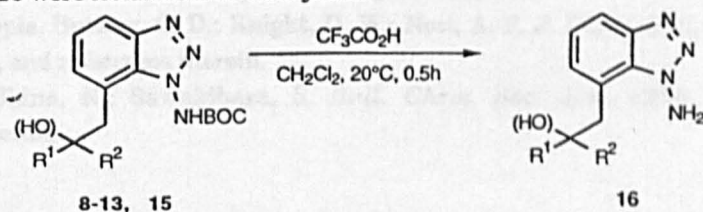
bromide was also very efficient, leading to an 85% isolated yield of the expected adduct **10**. Similar yields of the adducts **11** and **12** were obtained when benzaldehyde or 2-furfural were used as the electrophiles. A more rigorous test is the reactions of dianion **7** with enolizable aldehydes and ketones. These gave consistently lower returns. Thus, the adducts **13** and **14** from *n*-hexanal and citral were isolated in yields of 55% and 53% respectively. In contrast, ketones reacted slightly more efficiently; the product **15a** from acetone was formed in 70% yield while the corresponding cyclohexanone adduct **15b** was isolated in 62% yield.

TABLE: Reactions of Dianion **7** with Electrophiles^a



^a The electrophiles are given in brackets beneath the product structures; yields are isolated but unoptimised.

Finally, each of the foregoing adducts **8-13** and **15** has been successfully deprotected by brief exposure to trifluoroacetic acid in dichloromethane. After basification, the free 1-amino-benzotriazoles **16** were isolated in 75-95% yields.



No evidence for dehydration, even with the sensitive alcohols [*eg.* **11** and **12**] was

observed. The one exception to this was the citral adduct **14** which decomposed under these conditions; the addition of cation scavengers¹¹ failed to alleviate this.

The dianion **7** should therefore be of use in the elaboration of a wide variety of benzyne precursors; an illustration of the utility of this methodology is given in the following paper.

Acknowledgements

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A New Approach to Dihydrobenzofurans by Intramolecular Trapping of Benzyne by Hydroxyl Functions

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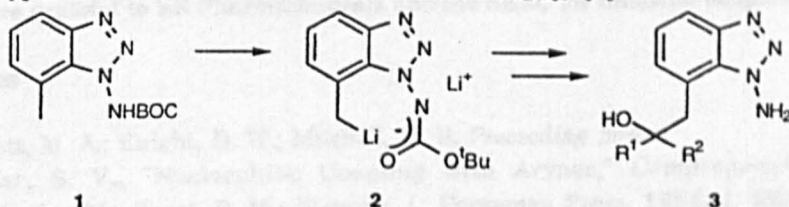
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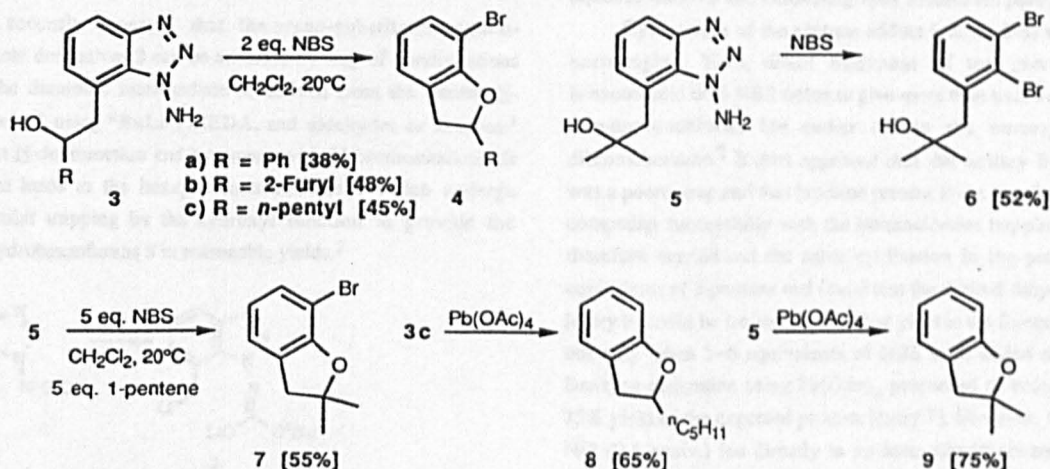
Abstract: The adducts **3**, derived from condensations of the 1-aminobenzotriazole dianion **2** and aldehydes or ketones, are converted into the corresponding benzyne upon exposure to either *N*-bromosuccinimide or lead(IV) acetate; intramolecular trapping by the hydroxyl group then leads to the dihydrobenzofurans **4**, **7**, **8** and **9** in 38-75% isolated yields.

In the foregoing paper, we describe the generation of the dianion **2** by double deprotonation of the *N*-BOC-1-aminobenzotriazole **1**, and subsequent condensations with aldehydes and ketones leading to the adducts **3**.¹ Herein, we report that these can be smoothly converted into the corresponding benzyne which are then trapped *in situ* by the flanking hydroxy function. The two major synthetic uses of benzyne are as Diels-Alder dienophiles and as electrophiles. Following the classic studies of Bunnett and his colleagues, the types of nucleophilic partners have been largely limited to amines (usually after deprotonation), enolates and α -lithionitriles.^{1,2} As arynes are soft acids, alcohols and alkoxides should be less reactive partners;² however, benzyne have been trapped efficiently by simple examples of both these types of nucleophiles^{2,3} as well as intramolecularly by phenoxides.⁴



The attraction of generating benzyne from 1-aminobenzotriazoles is the simplicity and mildness of suitable reagents, either *N*-bromosuccinimide or lead(IV) acetate.³ We were pleased to find that exposure of the aminobenzotriazoles **3a-c** to two equivalents of NBS at ambient temperature in dichloromethane led rapidly to the bromo-dihydrobenzofurans **4a-c**, which were isolated in the yields indicated.⁵ By contrast, the adduct **5** derived from acetone failed to cyclise under these conditions and instead, the dibromo derivative **6** was isolated in 52% yield. We reasoned that the more hindered hydroxyl function was not competing successfully with the bromine present in the reaction mixture. Therefore, 1-pentene (5 eq.) was added as a bromine trap prior to the addition of NBS. Now that the latter was the major

bromonium ion source, ca. 5 equivalents were required to drive the reaction to completion leading to the bromo-dihydrobenzofuran **7**. As an alternative, oxidation of the aminobenzotriazoles **3c** and **5** using lead(IV) acetate [1.1 eq., CH_2Cl_2 , 20°C]⁴ led smoothly to the less functionalised dihydrobenzofurans **8** and **9** respectively, in somewhat greater yields than with NBS.



This relatively brief approach appears to have considerable potential for the elaboration of a wide range of dihydrobenzofurans.⁶ The incorporation of an additional bromine atom in the final products **4** and **7** is a significant bonus as this should allow for the incorporation of a variety of additional substituents at the 7-position using either Pd- or Ni-catalysed coupling reactions or radical chemistry. Studies of these possibilities are in progress.

Acknowledgements

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N-Iodosuccinimide: A Superior Reagent for the Generation of Benzyne from 1-Aminobenzotriazoles

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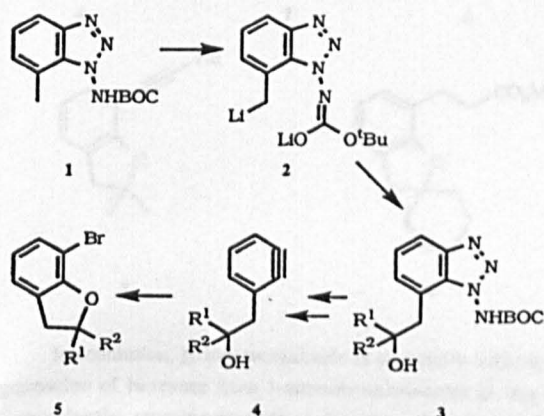
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Abstract: N-Iodosuccinimide [NIS] is a superior reagent for the generation of benzyne **4** from 1-aminobenzotriazoles containing *ortho*-hydroxyethyl groups; intramolecular trapping provides good yields of iodo-dihydrobenzofurans which can be further homologated by a variety of coupling reactions.

We recently reported that the *ortho*-substituted amino-benzotriazole derivatives **3** can be accessed by way of condensations between the dianionic intermediate **2**, derived from the parent N-BOC-triazole **1** using ⁿBuLi-TMEDA, and aldehydes or ketones.¹ Subsequent N-deprotection and treatment with N-bromosuccinimide [NBS] then leads to the benzyne intermediates **4** which undergo intramolecular trapping by the hydroxyl function to provide the bromo-dihydrobenzofurans **5** in reasonable yields.²



The oxidation of aminobenzotriazoles to benzyne using NBS was developed by Campbell and Rees during their seminal studies of this type of chemistry.³ As an alternative, lead(IV) acetate can also be used. However, in our initial studies, while this latter method provided somewhat higher yields of dihydrobenzofurans, these were unsubstituted at the 7-position and hence not readily amenable to further homologation. We have examined a variety of alternative reagents for effecting the generation of the benzyne **4** from the corresponding 1-aminobenzotriazoles and were pleased to find that by using N-iodosuccinimide [NIS], much improved yields of 7-iodo-dihydrobenzofurans were obtained. An anticipated bonus of this finding is that the iodine atom should be amenable to participation in many subsequent homologations, such as Heck reactions and palladium-catalysed couplings with a variety of organometallics.

The results obtained from the oxidations are collected in the Table. Entries 1 and 4 are examples of the typical yields [38–45%] of bromo-dihydrobenzofurans **5** obtained using NBS.² Yields of the less substituted examples, using lead(IV) acetate to generate the benzyne intermediate,^{3,4} are generally rather better [65–75%; entries 2 and 7]. However, both are exceeded by the excellent 92% yield obtained from the n-pentyl derivative using NIS [entry 3]. Similarly, the return from

cyclisation of the benzaldehyde adduct [entries 4 and 5] is improved from 38 to 81% using NIS. The reactions are simple to conduct: a solution of the aminobenzotriazole in CH₂Cl₂ is added dropwise to a solution of NIS (2.5 equiv.) in the same solvent at ambient temperature during ~10 min, then the whole is stirred for 2–3h before a simple aqueous work-up and chromatography secures the pure product.

Cyclisations of the acetone adduct [entries 6–8] were especially encouraging. Thus, direct treatment of the precursor amino-benzotriazole with NBS failed to give more than traces of the expected dihydrobenzofuran but rather led to the corresponding 1,2-dibromobenzene.² It thus appeared that the tertiary hydroxyl group was a poorer trap and that bromine present in the reaction mixture was competing successfully with the intramolecular trapping process. We therefore carried out the same cyclisation in the presence of five equivalents of 1-pentene and found that the desired dihydrobenzofuran [entry 6] could be isolated in a similar yield to the foregoing examples, but only when 5–6 equivalents of NBS were added during 1–1.5h. Benzyne generation using Pb(OAc)₄ proceeded as before and gave a 75% yield of the expected product [entry 7]. However, treatment with NIS (2.5 equiv.) led directly to an iodo-dihydrobenzofuran in 95% yield [entry 8]. Similarly, the cyclohexanone adduct [entry 9] failed to cyclise when treated with NBS, even in the presence of 1-pentene, but gave an 82% yield of cyclised product using NIS [entry 10].

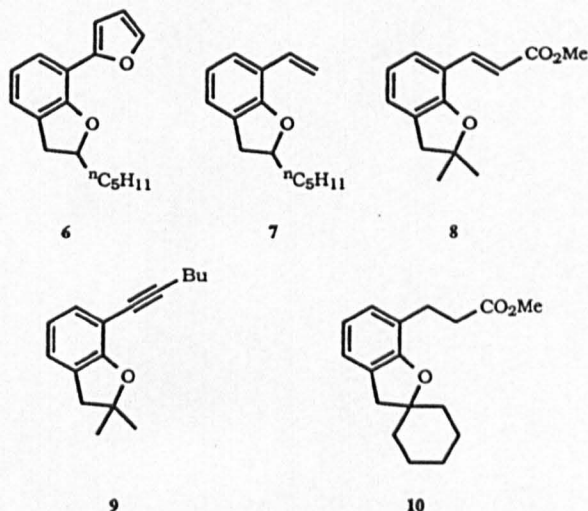
Table. Formation of Dihydrobenzofurans

Entry	R ¹	R ²	Reagent	X	% Yield ^a
1	n-Pent	H	NBS	Br	45
2	n-Pent	H	Pb(OAc) ₄	H	65
3	n-Pent	H	NIS	I	92
4	Ph	H	NBS	Br	38
5	Ph	H	NIS	I	81
6	Me	Me	NBS	Br	45 ^b
7	Me	Me	Pb(OAc) ₄	H	75
8	Me	Me	NIS	I	95
9	-(CH ₂) ₄ -		NBS	Br	~0 ^c
10	-(CH ₂) ₄ -		NIS	I	82

^a Yields refer to isolated products showing satisfactory spectroscopic and analytical data; ^b in the presence of 5 eq. 1-pentene; ^c with or without added 1-pentene.

Subsequent coupling reactions indicate the potential of these initial products. In general, the presence of an *ortho*-oxygen function is not helpful in many of these processes and good yields are often

only obtained from *ortho*-iodo derivatives.⁵ The iodo-dihydro-benzofurans proved eminently suitable for homologation using a variety of coupling reactions. Thus, palladium-catalysed coupling⁶ of the pentyl derivative (entry 3, Table) with both 2-tributylstannylfuran and ethenyltributylstannane led to the homologues 6 and 7 in 75 and 80% isolated yields respectively. A modified Heck coupling⁷ with methyl acrylate gave a 62% isolated yield of the cinnamate 8 from the acetone adduct (entry 8, Table) while reaction with 1-hexyne [(Ph₃P)₂PdCl₂, CuI, Et₂NH]⁸ led to an 87% isolated yield of the alkyne derivative 9. Radical addition was also possible; treatment of the cyclohexanone adduct (entry 10) with tributyltin hydride and AIBN (C₆H₆, reflux) in the presence of excess methyl acrylate⁹ gave a 55% unoptimized isolated yield of the Michael addition product 10.



In conclusion, *N*-iodosuccinimide is especially suitable for the generation of benzyne from 1-aminobenzotriazoles in this type of intramolecular trapping reaction. A bonus is that the iodine atom incorporated in the products facilitates subsequent homologation

reactions, based on Pd(0)-catalysed coupling reactions or radical generation. Other applications of this method of benzyne generation are being investigated.

Acknowledgements

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